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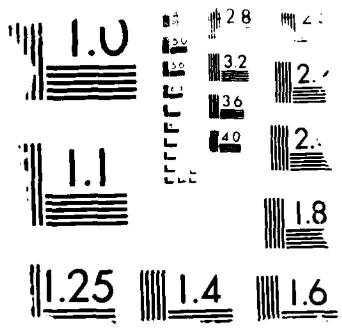
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ASSESSMENTS AND VIEWPOINTS ON THE BIOLOGICAL AND HUMAN HEALTH EFFECTS OF EXTREMELY LOW FREQUENCY (ELF) ELECTROMAGNETIC FIELDS.

Compilation of Commissioned Papers for the ELF Literature Review Project

American Institute of Biological Sciences
Washington, D.C.
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The AIBS Report Committee, in evaluating the post-1977 literature on extremely low frequency (ELF) electromagnetic field effects on human health and biota, solicited a spectrum of viewpoints and assessments on the subject from representatives of the scientific research community. This collection of 18 papers, representing the views of 29 scientists, were considered by the Committee in preparing its report, Biological and Human Health Effects of Extremely Low Frequency Electromagnetic Fields (ADA 152-731), for the Department of the Navy.

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P R E F A C E

The compendium that follows is a collection of topical resource papers compiled by a number of scientists contributing their expertise to a study conducted by the American Institute of Biological Sciences for the Naval Electronics Systems Command. The study was an evaluation and analysis of the extant professional literature published since January 1977 about the biological and human health effects of extremely low frequency (ELF) nonionizing electromagnetic radiation of consequence to the Department of the Navy's ELF Communications Program. The papers represent the opinion of the authors of the content of the literature they reviewed and their conclusions as to the meaning of that content.

These resource papers were reviewed and the author's conclusions evaluated by an AIBS appointed committee of experts, the Committee on Biological and Human Health Effects of Extremely Low Frequency Electromagnetic Fields. In addition, the Committee reviewed and evaluated books, research reports, project reports, articles and papers from peer-reviewed journals that discussed or described biological and human effects of nonionizing electromagnetic radiation in the frequency range of 1 to 300 Hz to produce its report. The report, "Biological and Human Health Effects of Extremely Low Frequency Electromagnetic Fields," was submitted to the Department of the Navy in March 1985.

The ELF study is another in a long history of AIBS programs bringing together the advisory resources of the bioscience community and Federal agency projects. The Institute expresses its thanks to the topical resource paper authors for their important contribution to the study and to the ELF Committee and advisors, and also recognizes the diligence of Molly Frantz, the AIBS Project Coordinator. We also express our appreciation to H. B. Graves, General Chairman of the report Committee, the study, and organizer of the resource paper effort. Thanks are extended to Cindy DeWeese whose assistance was invaluable to the completion of the project.

Donald R. Beem

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EFFECTS OF ELF FIELDS ON NEURAL DEVELOPMENT AND NERVE REGENERATION

Ernest N. Albert, Ph.D.
Gary Cohen, M. S.

The George Washington University Medical Center

NTRODUCTION

An extensive literature has accumulated on possible biological effects of xtremely low frequency (ELF) electric fields, especially in the areas of nimal behavior and physiology. In contrast, very little is known about ELF ields effects on developing nervous systems, although theoretical arguments xist for possible effects. Initial reports, including those with some dverse effects, need much further verification in order to determine how, if t all, neural development may be vulnerable to an environment increasingly ull of ELF fields.

While physical descriptions of these and other frequencies in the lectromagnetic radiation spectrum have existed for over a century, biological nvestigations of ELF field effects are quite recent in origin. ELF fields ay be the most heterogeneous of all forms of nonionizing radiation. Simple alculations show that their fields have wavelengths measuring in the housands of kilometers, and therefore, their wavelengths differ by this agnitude. Low frequencies also produce varying wave forms at any one requency of interest. Consequently, the problem of standardizing research at limited number of field parameters is likely to plague biological work for uite some time. Making generalizations about biological effects of ELF ields is dangerous, at best.

Although possible mechanisms of biological interactions are only a matter f speculation at this time, cellular activities which might be affected by LF fields are known to be critical in neural development. Although ELF ields have too little energy to break the covalent and hydrogen bonds so rominent in living organisms, they may well change the three-dimensional tructure of ions and molecules existing as either temporary or permanent ipoles (Adey 1981). Molecular conformation is of the utmost importance in

ELECTROMAGNETIC FIELDS AND CALCIUM EFFLUX

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The purpose of this manuscript is to analyze the body of experimental studies investigating the effects of electromagnetic radiation on the release of calcium ions from nervous tissue. These studies have drawn considerable attention and concern because of their implication that radio frequency and/or microwave radiation may measurably alter calcium efflux from nervous tissue; therefore, the electromagnetic radiation may also be altering basic cellular processes of neurons and/or neuroglia. Demonstration of positive effects holds both a promise and a threat: the promise of having a non-pharmacological tool in the clinical setting for health care and the threat that under certain conditions common electrical devices can be harmful to human and animal health.

In order to clarify the significance of the studies that will be reviewed and discussed, we should like to categorize--at the beginning--what these studies do not show. The reason for this is simple. As the experimental findings were presented, the focus was on the issues of experimental design, nature of data being gathered, and statistical methods employed to analyze data. By contrast, the implications of the findings were not addressed. In this highly specialized area of scientific investigation, an area requiring expertise in both physics and cell biology, much confusion exists between hard laboratory data and soft discursive conclusions drawn from the data. Therefore, the digressive material is dealt with at the outset.

1. None of the studies on electromagnetic field effects on calcium provide any evidence concerning the sizes and/or exchange half-lives of intracellular calcium pools. All intracellular calcium pools of eucaryotic cells (including those of nervous tissue) can be maximally labelled with ^{45}Ca after 1- to 2-h radiolabelling. Measurement of the sizes and exchange half-lives of these pools requires first, maximally labelling the cells; second, quickly and consistently washing the cells free of radiolabelling medium; and third,

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When these and other experimental difficulties are resolved, we may feel more confident about research in this important area, and either recognize significant ELF effects or allay any fears about adverse effects some investigators have reported.

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Thus, as has been true in other studies of potential neural developmental effects of ELF fields, researchers in the area of periphera' nerve regeneration have reached quite different conclusions. Species differences, as well as differences in frequencies and wave form, may explain these discrepancies, as may the details of experimental techniques. However, it may be true that more needs to be learned about standardizing the actual field strengths of ELF fields experienced by the animals or tissues of interests. While microwave research has been significantly improved by the calculation of the thermal specific absorption rate, no such technique exists in ELF fields research. Nerve regeneration studies, as well as the other topics of this discussion, will continue to be the victim of experimental discrepancies until some form of standardization can be found.

SUMMARY AND CONCLUSIONS

The extensive proliferation of ELF fields in the lives of countless millions of humans and animals is, by itself, reason enough for investigations of biological effects of these fields. A more critical area of biological effects can hardly be found than the development of nervous systems. Further, theoretical reasons exist for believing there may be a morphological basis for the behavioral and physiological effects already reported to occur. Changes in neuron number, or changes in ability of neurons to reach their proper targets, are likely to yield such morphological alterations. While some quite dramatic alterations have been reported, their inability to be replicated, in some instances, points to the special difficulties in exposure to ELF in standardized regimens using standardized animal or tissue preparation and standardized handling of these preparations. Solutions to some, but not all, of these difficulties might be found in the use of in vitro tissue culture systems with the use of similar electrical coils and/or plates. Our laboratory, as have others, is investigating rat dorsal root ganglia grown in Petri dishes which can be placed between simple electrical plates or within coils. If whole animal studies do continue, it may be useful to consider factors which are important in how animals respond to ELF fields, one of which is the ability to recover from any induced damage. Recovery periods need to be at least standardized, if not greatly reduced.

of each cross-section did not appear to be complete. Muscle testing was prone to errors in exact positioning of hind legs; and measured strengths may depend on factors other than the extent of nerve regeneration, such as animal size, age and pre-experimental activities. Cutting both sciatic nerves in each animal gives the investigators more data for each animal, but prevents one from having a control muscle or nerve in the same animal, which could be useful in both functional testing and neuronal histological evaluations. It might be more revealing to cut only one nerve and, instead, use the uncut nerve and muscle as a control rather than another animal.

A similar study by Orgel, O'Brien, and Murray (1984) failed to find any enhancement of peripheral nerve regeneration by ELF fields. This study does note, however, species differences, and important differences in ELF frequencies and wave forms. In this experiment, rats were divided into four groups: (1) nontreatment control group; (2) control group placed in an uncharged apparatus; (3) group given electrical exposure of one type; and (4) group given quite a different ELF field exposure. The former exposure group was subjected to 15-Hz pulses, with 380 μs positive-going and 24 μs negative-going. The latter exposure group was subjected to 72-Hz pulses, 200 μs positive-going and 6 ms negative-going. Field strengths were not given. Orgel et al. (1984) also exposed cats for a total of 12 weeks, placing them in harnesses for 10 h/day, 6 days/week, for either no exposure or exposure to ELF fields. The first control group was never placed in the harness. Animals were allowed free mobility the rest of the time. No gap was left between the two segments of the cut left common peroneal nerve. To measure the extent of regeneration in the single nerve cut in each animal, Orgel did histological analysis of the nerve as well as the ability of the nerve to conduct the retrograde transport of horseradish peroxidase (HRP), a substance whose reaction product can be visualized with light and electron microscopes. Also, electrophysiological recordings were made of the reinnervated muscles, comparing them with preoperative recordings.

In contrast to Ito and Bassett (1983), Orgel (1984) found no significant differences in nerve regeneration induced by ELF fields. No differences were found among the two control and two experimental groups in either axon diameters or densities, HRP transport to the spinal cord, or muscle compound action potentials.

without a gap. In this study the investigators cut the nerve in 73 of 77 rats. The animals were placed in body casts, and placed either inside magnetic coils (exposed animals) or at least three meters away (control animals) in the same room. The immobilized experimental animals were completely inside a pair of coils charged with single-pulses, 380 μs in duration and positive-going, at 72 Hz. Amplitude of the coil voltage was determined to be 15 mV, but the actual field strengths experienced by the rats were not given. Exposure, for as long as 14 weeks, was for either 12 or 24 h/day.

Ito and Bassett (1983) studied both the histology of the nerve and performance of reinnervated muscles (gastrocnemius and soleus) for the success of regeneration. Some, presumably representative, areas of nerve cross-sections were examined for axon density. Distance travelled past the cut stump was also recorded by viable axons. Qualitatively intracellular content was evaluated. The mean load lifted by both hind legs was also determined by fixing the hindlegs into a standard position and placing a load cell on the feet.

Ito and Bassett (1983) found that, in comparison to control rats, animals exposed for either 12 or 24 h/day had superior nerve regeneration. Experimental nerves had a greater migration of fibers past the distal stump; strangely, the actual distance was greater in rats given 12-h daily exposures than in those given continuous exposures. While distances travelled in the exposed animals' nerves were significantly greater in both experimental group than in control, there was no significant difference in the two experimental groups. Axon numbers and diameters were larger in experimental rats, but the actual figures were not given. Similarly, interaxonal collagen was simply stated as having "appeared greater" in exposed animals. Functional tests showed no differences in mean loads until 12 weeks of exposure, when exposed rats' hindlimbs had more than double the mean loads of controls. The four rats who were not operated upon but were placed in casts had less ability to lift loads than untreated rats, but the differences were not significant.

While these results seem clear-cut, certain aspects of Ito and Bassett's techniques are prone to error. However, this criticism may be directed at all attempts to study nerve regeneration in an in situ system. Specific details and raw data on axon counting are not given, and the histological examination

laboratory has made the strongest claims so far for ELF field effects on development.

Inevitably Delgado's findings (Delgado et al. 1982; Ubeda et al. 1983) will be called into question as other investigators try to replicate his findings. Such an attempt has already been started by Martucci, Gailey, and Tell (1984) who have found no abnormalities in their exposure of chick eggs while using experimental parameters similar to Delgado's. While it can be argued that minimal differences in wave forms, egg handling, or even strain differences in the chicks may be responsible for this discrepancy, it would suggest a much larger problem in exact reproduction of Delgado's techniques. No other major publications exist for purposes of comparison, although an abstract by Bootz et al. (1978) found only minimal effects on chicks exposed to 50-Hz fields at 30 kV/m. Chicks exposed for 43 weeks showed only reduced weights in comparison to controls, and no abnormalities were found in hatchlings.

ELF FIELDS AND PERIPHERAL NERVE REGENERATION

Great interest has developed recently in the possibility of enhancing *peripheral nerve regeneration* by exogenous electric fields, including ELF fields. While nerve regeneration has at least some differences with the original development of the peripheral nervous system, regeneration is thought to be dependent on some of the same processes, including directed axonal migration, Schwann cell direction, and interaction with muscle fiber membrane proteins (Seil 1983). During the last two decades investigators have cut a motor nerve, sutured it in place, and attempted to monitor regeneration by histological analysis of the nerve or the performance of the reinnervated muscle. While some of the investigators, using various electromagnetic parameters, have had varying successes, their explanation of experimental conditions has been so ambiguous as to defy analysis. Two recent reports--with quite different results--have more clearly specified experimental conditions, including the frequencies and wave forms of ELF fields used.

Ito and Bassett (1983) cut both sciatic nerves in female Sprague-Dawley rats and sutured them after leaving a one millimeter gap, thus avoiding the nearly impossible attempt of early investigators to realign nerve fibers

to be involved in normal cellular migration and development and could, by their absence, be a sole cause of the stunted development found by Delgado and coworkers (Delgado et al. 1982; Ubeda et al. 1983).

Finally, at all frequencies and magnetic field strengths, various abnormalities were found in the truncal nervous system, cardiovascular system, and somites, but these defects were always far less than those found in the cephalic nervous system.

In discussing their findings, Delgado et al. (1982) emphasized the particular potency of ELF fields at 100 Hz and 1.2 μT, comparing it to the "window effect" of a limited range of frequencies having specific effects, as proposed by Adey (1981). Consequently, greater emphasis on this frequency was made in the Ubeda et al. paper (1983). A much larger sample size (659 eggs) was used. No description of the wave form was given in the first paper: no drawings or rise time were provided for four wave forms. Now the claim was of only reduced glycosaminoglycans, not a total absence. Perhaps this reveals the laboratory's understanding that Alcian blue stains are very pH-sensitive, and at any one pH only some, and not all, glycosaminoglycans will be stained. All work used 100-Hz fields, with a pulse duration time of 500 μs, with magnetic field intensities ranging from 0.4 to 104 μT and rise time of 100, 42, or 2 μs. Also, to test effects from merely placing eggs inside the coil, a control group was placed inside an uncharged coil and compared with a group outside: no significant differences were found between the two groups.

The results of this second investigation showed a more narrow "window effect," with the most severe abnormalities, especially in the cephalic nervous system, at intensities of 1.0 and 13.9 μT. The term "window effect" seems to be appropriate here, since the wave forms and not thermal sensitivities appear to be responsible at these low intensities. One of the 100-Hz pulses with a rise time of 42 μs was the most potent in causing abnormalities in all systems studied, especially when the magnetic strengths was 1.0 μT. As with the first experiment, all systems were affected, but the most vulnerable was the cephalic nervous system. And again, alternations of glycosaminoglycans were considered a possible cause of these severe inhibitions of chick embryogenesis in which minimal neuronal differentiation was sometimes found. Having observed extensive areas of abnormal development, necrosis, and poor cellular adhesion throughout the embryos, Delgado's

standardizing exposure conditions and periods of recovery. The issue of recovery is critical. Subtle cerebellar deficits were found by Sikov et al. (1984) to be recoverable within a week, for example, and slight morphological changes may be associated with such physiological deficits as decreased righting reflexes and geotropism. In our study we also did not observe the gross reductions in animal weights or motor control found by Hansson (1981); this may again be due to differences in exposure conditions or recovery periods, or may be a species difference.

ELF FIELDS AND CHICK EMBRYOGENESIS

Perhaps the most startling findings in the field of ELF field effects on neural development are those from the laboratory of Delgado. Two publications have reported severe impairment of chick embryogenesis from the exposure of very weak ELF fields (Delgado et al. 1982; Ubeda et al. 1983).

The first paper reported that a total of 68 fertilized chick eggs, from white Leghorn hens, were incubated at 38° C and 55% humidity for 48 h. Two experimental eggs during each experiment were placed inside a copper coil, while one control egg was placed inside the same incubator but outside this coil. Three frequencies were used: 10, 100, and 1,000 Hz, with current adjusted to provide magnet strengths of 0.12, 1.2, and 12 μT at each frequency. These magnetic strengths were all well below the earth's own magnetic field strength. The 26 control and 49 exposed embryos were then fixed and scored for development by the Hamberger and Hamilton criteria for chick embryos.

While 22 of the control eggs (84.6%) were graded normal after 48 h, 33 of the exposed eggs (78.5%) were graded abnormal. By far, the greatest abnormalities were from exposure at 100 Hz, and at all frequencies the cephalic nervous system was most commonly affected. Specifically, at 100 Hz the eggs exposed to the intermediate magnetic strength (1.2 μT) were the most affected: all six eggs were grossly underdeveloped, and the central nervous systems were no more than a thickened plate of ectoderm. At 48 h, a fully closed neural tube should be present in chick embryos, with division of the brain into its three primary vesicles. Staining with Alcian blue (pH 3) revealed the complete absence of glycosaminoglycans in the intercellular matrix in eggs exposed to 100-Hz, 1.2-μT fields. These molecules are thought

After a one-week recovery period, pups were ear-coded by Battelle and sent to our laboratory for electron microscopic analysis. For further details of the exposure procedure see Kaune (1979).

Electron microscopic analysis was done single-blindly on male and female rats identified only by code. Included in the electron microscopic studies were ultrastructure of the cerebellar Purkinje cells and the hippocampal pyramidal cells. Also, quantification of synapse density in the molecular layer of the cerebellar cortex was done (Albert et al. 1984).

Results showed no significant differences in synaptic density between control and exposed rats, although exposed females showed a nonsignificant increase of 9.3% over control females. Sampling size, however, was too small to make final conclusions on synaptic counts, since only a total of 16 rats was evaluated.

Albert et al. (1984) found that Purkinje cells in two of the exposed rats showed moderate alterations in ultrastructure. These alterations consisted of short, dilated smooth membrane cisterns occurring in stacks of two to five. Some Purkinje cells had only very few of these structures, however. Although these structures have a greater resemblance to sublemmal cisterns, we have chosen to associate them with the lamellar bodies found by Hansson (1981). It must be pointed out that the size as well as the number of these lamellar structures were insignificant as compared to those reported by Hansson. Further studies of Purkinje cells in animals sacrificed and preserved without delay after exposure may resolve the discrepancy between the results obtained in these two laboratories.

Our investigation of the pyramidal cells of the hippocampus similarly revealed only minimal alterations. Pancake-like membranous structures, very few in number, were seen in only two of the 16 experimental animals. In all other respects, pyramidal cells of all control and experimental rats appeared identical. The pancake-like structures were clearly associated with the rough endoplasmic reticulum. We conclude that somehow the rough endoplasmic reticulum could have lost its ribosomes to form these structures, although we do not propose how this might have occurred. Again, the very small numbers of structures found make physiological deficits unlikely.

Further studies of the brains of animals exposed to ELF fields may not resolve the discrepancies between our laboratory and Hansson's without

any electric field, did not keep their coats clean, and "appeared slow in movement." This motor deficit led to histological analysis of the rabbits' cerebellum. This analysis revealed cerebellar ultrastructural changes of startling magnitude in the exposed rabbits: reduced arborization of dendrites, reduced number and size of Nissl bodies (rough endoplasmic reticulum), reduced numbers of microtubules and mitochondria, and increased microfilaments. No actual numbers or percentages for these changes were given. However, the most dramatic effect was the existence in Purkinje cells of 500 to 1,200 lamellar bodies which were never found, in any number, in control animals. These lamellar bodies appeared to be stacks of tubular profiles of smooth endoplasmic reticulum. In contrast, only a few profiles of normally plentiful rough endoplasmic reticulum, as noted above, could be found.

Hansson suggested malnutrition could be the ultimate problem. This explanation is plausible in light of the severe weight reduction noted in experimental animals, but food intake records were not available for substantiation. The outdoor exposure of these rabbits also raises serious questions regarding effects of uncontrolled temperature, humidity, etc. There is almost no quantification of results or, indeed, of the total number of animals or electron micrographs examined. The claim of "marked neuronal alterations were observed in several [other] parts of the brain and retina" is made without presentation of any evidence.

Hansson's work (1981) does represent a beginning in the study of the ultrastructure of developing nervous systems, in spite of its methodological difficulties. The cerebellar cortex, including its Purkinje cells, represents an excellent model for studying possible neural developmental effects, since the basic outline of its development is well researched (Altman 1972). A study of rat brains, including the cerebellar cortex, in animals exposed to a 60-Hz field has been recently completed in our laboratory with quite different results from those reported by Hansson.

Albert et al. (1984) were provided exposed female Sprague-Dawley rats by the Battelle Pacific Northwest Laboratories. Unperturbed 60-Hz fields were used at 100 kV/m; but it was estimated that the animals experienced only 65 kV/m due to perturbation by lexan cages. Female rats were then mated with unexposed males and exposure was continued throughout gestation. After birth, mothers and pups, in litters culled to 8 pups, were exposed until day 21.

stress that caused the increased death rates but did not offer any details on behavioral, physiological, or pathological observations on the exposed animals.

The findings of Marino and others (1976, 1980) have not been repeated by investigators looking at rodents developing in the presence of 60-Hz fields. For example, Fam (1980) exposed mice to 240-kV/m, 60-Hz fields for three months and found no developmental effects of any kind in the offspring.

Perhaps the most thorough study was undertaken by Sikov et al. (1984). They exposed Sprague-Dawley rats to 60-Hz fields, at 100 kV/m, 20 h/day on a 12:12 h light:dark cycle, throughout mating, pregnancy and up to day 25 after birth in one experiment. Using specially designed cages for studies of ELF effects on rats, possible effects from a corona discharge and ozone production were eliminated by cage dimension and arrangement. Only the first generation of offspring were evaluated for a host of possible developmental abnormalities including infant mortality and body weight. Reproductive capabilities of the pregnant mothers were also evaluated.

In contrast to Marino et al. (1980), Sikov et al. (1984) found no lasting differences in exposed animals in any aspect of reproduction and development, including body weights, fetal abnormalities, brain pathology, postnatal mortality, or a variety of behavioral and neurological tests. However, significant transient differences were found in motile behaviors and the righting reflex in 14-day-old rats; at 21 days of age the differences were no longer significant, raising the possibility of neurological repair of potential ELF field-induced damage.

ELF FIELDS AND NEURAL DEVELOPMENT

Hansson (1981) could justifiably say in his report that "No morphological study has been published on possible structural effects on the nervous system [by electric fields]." In an outdoor setting, Hansson exposed female albino rabbits to 14-kV/m lines, at 50 Hz. A second group was placed next to an open disconnecting switch (presumably for corona effects), a third group was surrounded by a Faraday's cage, and a fourth group of rabbits was placed outside a measurable electric field.

Exposure of females began sometime (unspecified) after mating, and offspring were subsequently exposed for the first 7-1/2 weeks after birth. Exposed rabbits reached just over half the weights of animals kept away from

immiscible liquids: dextran and polyethylene glycol. Cells were withdrawn from the upper phase, i.e., the dextran, and measured for concentration. Exposed cells were then compared with control cells. This allowed analysis via cell concentrations, and was independent of cell numbers. Exposed cells showed a significant change in their partitioning behavior between the two liquids. Presumably, this change in partitioning can result from either a change in membrane molecular composition or molecular charge. Such an *in vitro* system, which had previously detected mitotic delays and reduced oxidation in amoebae exposed to 60-Hz fields (Marron, Goodman, and Greenebaum 1978), allows numerous advantages of experimental design which may be applied to work on ELF field effects on neural development.

ELF FIELDS AND GENERAL DEVELOPMENT

Until the 1980s, only the most general aspects of animal development were studied in regard to possible ELF effects. Marino et al. (1980) exposed three consecutive generations of mice to 60-Hz fields. The mice were exposed continuously, 24 h/day, with a 12:12 h light:dark cycle, from mating through the 119th day of life of the third generation. The animals were in four different groups: a 15-kV/m vertical-field test group, a vertical-field control group (via grounding of plates), a 10-kV/m horizontal-field test group, and a horizontal-field control group (also via grounding). In comparison to their respective controls, mice exposed to vertical fields exhibited increased infant mortality rates in all three generations, while mice exposed to horizontal fields showed increased infant mortality only in the first generation. Body weights were also measured, but no consistent effects were found; in fact, females of the third generation exposed to vertical fields were significantly heavier than the control females.

In a previous experiment with similar parameters, this same laboratory had measured decreased body weights in all three generations and had also measured increased infant mortality in all three generations (Marino, Becker, and Ullrich 1976). The authors felt that the earlier experiment was victimized by various sources of experimental error, such as field changes resulting from mechanical vibration. Vibration was limited by separating the cages from aluminum plates by the placement of foam rubber sheets. In conclusion, Marino suggested a "nonspecific action of the electric field" producing a fatal

biological membranes, in which the fluid-mosaic model of Singer and Nicholson (1972) stresses the importance of noncovalent interactions. Further, neurons maintain at their membranes a 70 to 90 mV potential difference which--across a membrane only 75 A° thick--represents field strengths of about 10^7 V/m. Such a potential difference, whose maintenance requires a significant portion of cellular energy, could be altered by exogenous electric fields. Also, magnetic fields created by ELF fields may affect cellular activities involving diamagnetic ions, most importantly Fe^{+2}. Animal tissues have a permittivity to magnetic fields not much different from that of air.

The field of neural development is one of the most active areas in contemporary biological research. It is a difficult field because of the unique complexity of the final products, especially in mammals. However, a number of basic mechanisms of neural development have been proposed. Some of these mechanisms may be vulnerable to ELF fields (Jacobson 1978).

Neuronal proliferation, migration, and selective death are critical in neural development, and may be regulated by receptor-mediated factors taken up at cell membranes (Liu 1981). Steroids, including sex hormones, also play a role in neural development by acting via noncovalent interactions with cytoplasmic receptors, which are then translocated to the nucleus (McEwen 1983). Long journeys of neurons and their processes may involve poorly understood interactions with extracellular guiding proteins, such as fibronectin and laminin (Liu 1981). Formation of the correct synaptic connections seems to depend on the disposition of membrane macromolecules which were inserted via Golgi-derived coated vesicles, and then were left to find their appropriate location in the post-synaptic cell membranes (Altman 1971).

Therefore, various activities in neural development are dependent upon conformation of molecules and their noncovalent interactions with each other--any or all of which may be affected by ELF fields. Experimental support for the effects of ELF fields on membrane associations in nonneuronal cells has come from a long series of work on fungi by Marron, Greenebaum and others (Marron et al. 1983). Marron exposed Physarum polycephalum amoebae to sinusoidal 60-Hz fields, at 1 V/m, applied via stainless steel electrodes placed directly in the growth media. Perpendicular magnetic fields were 0.1 mT. Centrifuged cells were placed into solutions containing two

measuring the kinetics of radiolabel efflux for at least an hour at preferably 1- to 2-min intervals (in fact, 15- to 30-s intervals are advised during the first 5-min chase incubation). Plots of the percentage of cellular radioactivity retained after each interval as a logarithmic function of time always yield curved lines which, when analyzed, are generally found to be accounted for by the presence of at least two major, intracellular calcium pools with different exchange half-lives (Borle 1972; Eilam and Szydel 1981; Kondo and Schulz 1976; Lazarewicz et al. 1977; Lopez-Rivas and Rozengurt 1983).

It is important to bear in mind that the only definitive information contained within the kinetic data is that at least two pools of exchangeable, intracellular calcium exist (if there was only one pool, the plot would be a straight line). Accordingly, when investigators report that their data indicate the presence of two or more pools, they mean, in fact, that the kinetic data is best accounted for by the assumption of a particular number of pools with different exchange half-lives. The two kinetic pools generally indicated by the kinetic data are commonly interpreted as representing the free, cytoplasmic calcium and the calcium sequestered within the endoplasmic reticulum and mitochondria, with the former pool having the briefest exchange half-life and the latter pool having the longest exchange half-life.

None of the investigators in the field of radiation-induced effects have yet employed or developed experimental equipment which can collect multiple aliquots of medium during chase incubation of radiolabelled cells or tissue slices. Thus, no data is available on the effect of electromagnetic radiation on the number, sizes, and exchange half-lives of intracellular calcium pools. The absence of such data is significant; it means we have no knowledge of whether electromagnetic radiation affects, even transiently, the cytoplasmic level of free calcium. It is changes in the size of this pool which are known to be associated with calcium-dependent cellular processes (Hems and Whitton 1980).

2. None of the studies with positive results provide any evidence demonstrating that field-induced changes in calcium efflux are even temporally associated with changes in calcium-dependent cellular processes (in particular, neurotransmitter release). Thus, no evidence exists to support or even speculate that electromagnetic radiation can alter cellular events through modulation of calcium metabolism.

3. None of the studies provide any evidence concerning the size and approximate average exchange half-life of extracellularly-bound calcium. Under the best of circumstances (that is, in studies where investigators are not plagued with the problem of exposing cellular material to radiation in as consistent and rapid a fashion as possible prior to measuring calcium efflux) it is difficult to even approximate the size and exchange half-life of all extracellularly-bound calcium because of the extreme brevity of the half-life (i.e., 5 to 15 s) (Kondo and Schulz 1976). In a radio frequency-radiation experiment where an investigator is working with just two cellular samples, one a control and the other an experimental, it requires a minimum of 2 to 3 min to wash both labelled samples free of radiolabelling medium, properly position the samples in the exposure and sham-radiation chambers, close all doors to the radiation and incubation chambers, and finally begin exposure to electromagnetic radiation. The time constraints of this protocol insure that all the radiolabelled calcium bound to extracellular sites at the end of the radiolabelling period will be exchanged by mostly non-radioactive calcium during the washing steps. Furthermore, even before the exposure period is about to begin, at least some of the intracellular, radiolabelled calcium has already exited the cells. The released radiolabelled calcium is rapidly distributed between extracellular sites for calcium and the free pool of calcium ions in the medium. When the amount of radioactivity in both the bathing medium and the cells (or tissue) is measured after an exposure interval of 20 to 30 min, the measurements represent, in effect, the non-equilibrium distribution of the radiolabelled calcium between the cellular and medium compartments at the end of the exposure period.

All published studies of radiation-induced effects on calcium efflux from intact, cellular material are fundamentally reports of data on the non-equilibrium distribution of radioactive calcium between the cellular and medium compartments. Just as the data cannot resolve the effects of radiation on the distribution in intracellular calcium, it cannot resolve unequivocally the effects on the size and average exchange half-life of extracellularly bound calcium.

As a result of primarily physical limitations of the available equipment, investigators cannot make rapid and multiple measurements of calcium efflux from cells or tissues exposed to non-ionizing radiation. Consequently, no

data exist on radiation-induced effects on the size, number, and exchange half-lives of intra- and extracellular calcium pools. Instead, almost all of the available data pertain only to radiation-induced effects on the non-equilibrium distribution of radioactive calcium between the cellular and medium compartments.

The most major studies of radiation-induced effects began with the report by Bawin, Kaczmarek, and Adey (1975) that amplitude-modulated, 147-MHz radiation increases calcium efflux from chick forebrains. Brain tissue was incubated throughout each experiment in a physiological salt solution containing glucose. Each forebrain was divided along the longitudinal fissure immediately upon excision. The paired hemispheres were weighed, radiolabelled for 30 min with radioactive calcium, repeatedly washed, and concurrently incubated for 20 min with one hemisphere in the presence of and the other in the absence of field radiation. Efflux from each hemisphere was determined as radioactivity released/gm brain tissue and the ratio of the irradiated/sham irradiated determinations (for each matching pair of hemispheres) were calculated. Bawin and his coworkers reported in this initial study that when the amplitude modulation frequency is 11 and 16 Hz, calcium efflux is 15% and 18% , respectively, greater than that of control efflux ($p < .01$).

Bawin and Adey (1977) extended their initial findings by showing that with the same experimental protocol, calcium efflux was enhanced by 9 to 10% when the chick forebrain was exposed to a 450-MHz field, amplitude modulated at 16 Hz and with a field intensity of 0.5 and 1.0 mW/cm^2. Further experiments (Bawin, Adey, and Sabbot 1978a) showed that lanthanum ions, which displace extracellularly-bound calcium ions and block voltage-regulated calcium-ion channels in the cell membranes, inhibit the enhanced calcium efflux induced by the 147-MHz field. Finally, these investigators concluded their studies of chick forebrain hemispheres with reports (Bawin, Sheppard, and Adey 1978b; Sheppard, Bawin, and Adey 1979) that the 147-MHz field-induced effects are a function of not only the amplitude modulation frequency, but also the field intensity (being statistically significant at field intensities of 0.1 and 1.0 mW/cm^2, but not at field intensities of 0.05, 2.0, and 5.0 mW/cm^2).

The results of the studies by Bawin, Adey, and their coworkers were replicated and expanded in extensive studies conducted by Blackman and his colleagues (1979, 1980a, 1980b). Their experimental protocol with chick

forebrains followed as closely as possible that of Adey's group, with one notable exception in experimental design being introduced in the last two studies. This exception is worthy of elaboration at this point. For every set of exposure conditions, Blackman's group conducted--in essence--two separate sets of experiments. In one set of experiments, a forebrain hemisphere was exposed to radiation and the matching hemisphere served as a control by being co-incubated outside the exposure chamber. In the other set of experiments, a forebrain hemisphere was sham exposed in the exposure chamber and the matching hemisphere served again as a control by being co-incubated outside the exposure chamber. Calcium efflux was measured for each hemisphere as radioactivity-released/gm of brain tissue. Following calculation of all exposed/control and all sham exposed/control ratio values, parametric statistical analysis was applied to the two sets of ratio values.

Blackman and his coworkers' first report confirmed increased calcium efflux (in the 10 to 15% range) by a 147-MHz field, amplitude modulated at 16 Hz and applied at a field intensity of 0.75 mW/cm^2; by contrast, no field-induced effect was observed with a field intensity of 2.0 mW/cm^2. Their second report stated that with a 147-MHz field sinusoidally amplitude-modulated at 16 Hz, increased efflux is observed with a power density of 0.83 mW/cm^2, but not with power densities of 0.11, 0.56, 1.11, and 1.38 mW/cm^2. Their third report showed that with a 50-MHz field sinusoidally amplitude-modulated at 16 Hz, increased efflux is observed in two power density ranges, one spanning 1.44 to 1.67 mW/cm^2 and the other including 3.65 mW/cm^2. Comparison of data from the last two studies showed that field-enhanced efflux occurs when the rate of energy absorption is 1.3 to 1.4 mW/kg.

All of the experiments with paired hemispheres of chick forebrain have the design advantage of comparing calcium efflux from anatomically identical, contralateral brain tissue samples. This singular design advantage is, however, significantly offset by the fact that each forebrain hemisphere weighs roughly 1.0 gram and has dimensions of approximately 1 cm. It has been recognized for some time that if animal-tissue slices with dimensions greater than 1 to 2 mm are incubated in physiological medium, such dimensions do not permit adequate diffusion of nutrients and oxygen to the cells in the center of the tissue slice nor adequate diffusion of catabolic waste products out of

the tissue slice. Consequently, it is commonly appreciated that _in vitro_ incubation should be conducted with tissue slices having 1-mm dimensions (and, in instances where it is feasible, to work with partially or completely dispersed cell preparations) bathed in a large excess of nutrient-rich medium. All of the pioneering studies by these two groups of investigators were performed on 1-gm masses of brain tissue bathed in an equivalent volume of medium (i.e., 1.0 ml).

As has already been discussed, each data point gathered in these studies merely measures a non-equilibrium distribution of radioactive calcium between the forebrain hemisphere and the bathing medium. Nonetheless, the extent to which the distribution can serve, even indirectly, as a monitor of field-induced effects on living nervous tissue depends upon optimal maintenance of cellular metabolism throughout the duration of _in vitro_ incubation. This fundamental criterion is simply not satisfied with the use of chick forebrain hemispheres.

If the argument is advanced that the field-induced effects are due exclusively to field perturbation of calcium binding to extracellular sites, then it follows that similar effects may possibly be observed with aldehyde-fixed samples. Such preparation eliminates the experimental variability in the data rising from the variable necrosis of neurons and neuroglia in the forebrain hemispheres during the 20-min exposure period (however, fixation would alter the number and exchange half-lives of intracellular sites).

The studies conducted by Adey and Blackman and their colleagues are also flawed in the presentation and analysis of data. Measurements of CPM or DPM are not presented in any of these publications. The absence of these data precludes any attempt by other investigators to critically evaluate the findings. This is because the data in all these early studies are reduced to ratio or percentage values; and it is these values which are subjected to parametric statistical analysis involving a t or F distributions. Myers and Ross (1981) have criticized such an analytical approach on the basis that such a conversion of data points into ratio or percentage values may artificially create an asymptote or ceiling of variance.

In support of the argument advanced by Myers and Ross, consider the data presented in Table 1. These data were obtained from 20 separate experimental

runs conducted with paired chick forebrain hemispheres in our laboratory (Albert et al. 1980) All procedures were reproduced as closely as we could manage to those employed by Adey's group for measuring field-induced effects on calcium efflux; exposure was to a 16-Hz sinusoidally amplitude-modulated, 147-MHz field with a field intensity of 0.75 mW/cm^2. Calcium efflux is expressed in Table 1 as cpm radioactive calcium released/gm tissue under exposed and control conditions. The calcium efflux data for exposed and control conditions given in each row of Table 1 pertain to a matching pair of forebrain hemispheres.

TABLE 1

Experiment Number	cpm ^{45}Ca Released/gm Tissue in Exposed Chamber	cpm ^{45}Ca Released/gm Tissue in Control Chamber	Exposed/ Control Ratio
1	5,827	6,592	0.88
2	7,541	9,958	0.76
3	6,854	7,609	0.90
4	7,295	7,109	1.03
5	5,481	8,563	0.64
6	6,217	5,804	1.07
7	4,935	8,217	0.60
8	4,792	7,120	0.67
9	6,192	11,500	0.54
10	7,760	10,522	0.74
11	6,981	8,615	0.81
12	5,288	4,423	1.20
13	8,517	7,400	1.15
14	8,940	8,962	1.00
15	4,769	7,120	0.67
16	10,017	8,034	1.25
17	5,774	8,200	0.70
18	7,271	5,442	1.34
19	8,117	5,917	1.37
20	7,065	6,929	1.02

Albert et al. 1981.

Application of a two-tailed Student's t-test to the raw data in Table 1 (that is, analysis of the difference between the cpm released/gm tissue data for the exposed condition with that for the control condition) shows that no significant difference exists between the two columns of data. When, for each row in Table 1, the radioactive calcium released/gm tissue in the exposed condition is divided by the corresponding value representative of the control condition, we find the average ± standard deviation value of this ratio from the 20 separate measurements to be 0.92 ± 0.26. Analysis of these 20 ratio values by a Student's t-test also indicates that no significant difference exists between calcium efflux under exposed or control conditions. However, application of the Student's t-test to the the inverted (i.e., reciprocal) ratio values yields a t-statistic of 2.37, a magnitude which suggests that the field-induced 8% inhibition of calcium efflux is statistically significant at the 98% confidence level.

It is possible to challenge that this failure to replicate the findings of Adey and Blackman and their colleagues is a failure on our part either to adequately reproduce all experimental conditions or to conduct the experiments with appropriate expertise. However, it is not possible to challenge the fact that whereas parametric statistical analysis of raw data shows no field-induced effects, similar analysis of ratio values yields one conclusion if the exposed/control ration values are analyzed and an opposite conclusion if the control/exposed ratio values are analyzed. In sum, parametric statistical analysis of ratio values yields suspect conclusions.

The exceptional design features of the 1980 reports by Blackman are also questionable, especially since the positive sets of findings appear to be dependent on the use of such design features. Blackman et al. argue in these two studies that the findings demonstrate narrow power-density ranges in which 50- and 147-MHz carrier signals, amplitude modulated at 16 Hz, stimulate calcium efflux. However, as discussed at length by Myers and Ross (1981), the mean exposed/control and sham exposed/control ratio values vary with the power-density levels selected in the two studies.

In those instances where a statistically significant, positive effect is indicated, it is not because peaks of mean exposed/control ratio values exist but nadirs of mean sham exposed/control ratio values. Blackman et al. do not clarify the theoretical necessity of distinguishing between a sham-exposed

condition and a control condition. If it is suggested that these two conditions are not experimentally equivalent, then this implies that the physical factors influencing calcium efflux inside field-free exposure chambers are different from those influencing calcium efflux outside such chambers. In other words, at least one experimental variable exists whose identity and site of influence (i.e., either inside or outside the exposure chamber) is unknown and, therefore, whose control by individual investigators is not possible. If this is indeed the case, then it also follows that no justification exists for comparing a particular set of exposed/control ratio values with the companion set of sham-exposed/control ratio values that an investigator determines during the same time interval in a lab. This is because there is no way of knowing whether the unidentified environmental factor or factors remain constant during the several-week period required to generate all the exposed/control and sham exposed/control data for a specified exposure condition. In sum, acceptance of a distinction between a control and a sham-exposed condition is tacit admittance that adequately controlled experiments cannot be conducted.

Adey and his coworkers have recently extended their initial studies with chick forebrain tissue with studies of calcium efflux from awake cat cerebral cortex (Adey, Bawin, and Lawrence 1982) and rat synaptosomes (Lin-Liu and Adey 1982). They report enhanced calcium efflux during exposure to 450-MHz fields, sinusoidally amplitude modulated at 16 Hz. The effective power density for the cerebral cortex study is 3.0 mW/cm^2, and that for the synaptosome study 0.5 mW/cm^2. Let us consider first the cerebral cortex study. The experimental protocol consists of radiolabelling cortex tissue by bathing it in a well for 90 min and then completely exchanging the medium in the well every 10 min during a 210-min chase-incubation period. The data gathered in control experiments are used to determine, by linear regression analysis, an equation with exponential terms that best describes the kinetics of calcium efflux. Such analysis suggests, as discussed in the beginning of this critique, that the kinetics are most simply accounted for by the assumption of at least three calcium pools with different exchange half-lives. In experiments where field-induced effects are monitored, the duration of field exposure is 1 h beginning after a 90-min chase incubation. Field-induced effects are assessed by the extent to which the exposure kinetics deviate from the control kinetics predicted by linear regression analysis.

The fact that the cerebral cortex is not repeatedly washed free of radiolabelling medium at the beginning of the chase-incubation period means that there is an incremental, as opposed to an abrupt, transition from the radiolabelling period to the chase incubation period. The initiation of field exposure 90 min into the chase-incubation period signifies that field exposure occurs essentially during the terminal phase of calcium efflux. The investigators do not provide any cpm or dpm data nor any data concerning the percentage of radiolabelled calcium released after a 90-min incubation. However, by their own account in the beginning of the Results Section, they do indicate that the efflux kinetics may be accounted for by the assumption of three pools, and that after a 90-min chase incubation, efflux represents essentially an exchange from the pool with the longest exchange half-life. As explained in the beginning of this article, such a pool most likely represents an intracellular pool. The experimental design is thus testing the effect of microwave radiation on the calcium pool with the longest exchange half-life.

The results of the study do not show, contrary to statements in the abstract, increased calcium efflux during and after field exposure. By contrast, what the results do show, and what the authors confirm in the text on pages 301 and 302 (Adey et al. 1982), is that field exposure increases (with a confidence level of 0.986) the mean relative variance of individual readings taken during and after field exposure. The authors do not directly contend that statistical analysis confirms an increase in calcium efflux during and after field exposure, but rather an increase in the deviation of data points from predicted values. In sum, it is not evident from the findings presented if the field exposure genuinely enhances calcium efflux from the cerebral cortex or merely enhances the extent of fluctuations in the rate of efflux.

We may now consider the synaptosome study by Lin-Liu and Adey (1982). This study could be regarded as being outside the purview of this presentation, as it is not a study of calcium efflux from intact nervous tissue cells and at a microwave frequency. Nevertheless, it offers important information. Synaptosomes are the vesiculated, membrane-bound remains of synaptic terminals, and as such, may be regarded as anatomically and functionally intact cellular material. The investigators characterize calcium efflux from rat synaptosomes exposed to 450-MHz microwaves applied with a

field intensity of 0.5 mW/cm^2. The 450-MHz radiation is applied in continuous wave form, sinusoidally amplitude modulated at 16 Hz, and sinusoidally amplitude modulated at 60 Hz. In calcium efflux experiments, the synaptosomes are radiolabelled with ^{45}Ca for 15 min, applied to a Millipore filter, washed once, mounted on a perfusion apparatus, and finally perfused with calcium-free medium at a rate of 1.0 ml/min for 45 min with the perfusate collected at one-min intervals. Field exposure is applied for 10 min beginning at 16 min after the onset of perfusion.

Lin-Liu and Adey (1982) report that calcium efflux from the synaptosomes is biphasic. Statistical analysis of the data is thus predicated on the (reasonable) assumption of two pools of released calcium under all experimental conditions. Field-exposure effects are determined by comparing the rate constants for the two pools under control versus field-exposure conditions. Their results show that under control conditions the rapidly released pool has a half-life of 2.7 min and the slowly released pool has a 16-min half-life. Exposure to continuous wave or 60-Hz, modulated 450-MHz microwaves does not significantly alter either half-life. However, exposure to 16-Hz modulated microwaves increases the half-life of the slowly released pool to approximately 25 min.

It is to be expected from their experimental protocol that field exposure does not affect the half-life of the rapidly released pool, since almost all of that pool is released by the time field exposure begins 16 min after the onset of perfusion. However, roughly one-half of the slowly released pool has also been replaced by the time field exposure begins. Since their data analysis is conducted by non-linear curve fitting to a two-phase exponential function for all 1.0-min data points (excluding the first three points), it is likely that the investigators have underestimated the field-induced increase in the half-life of the slowly released pool. This is because the field-induced increase is occurring only for a 10-min period within the 42-min period of analysis while the computer analysis works on the assumption of a constant half-life for the pool throughout the perfusion period.

The results of this study raise some questions. The investigators note at the beginning of the Results Section that, although the synaptosomes are not washed completely free of radiolabelling medium just before perfusion, this practice does not lead to variable half-lives of the calcium pools. This is a

dubious contention. If the synaptosomes are not consistently washed completely free of radiolabelling medium just before perfusion, they will continue to be radiolabelled to minor (and variable) extents during the first few minutes of perfusion. Consequently, the less complete the washing of the radiolabelling medium just before perfusion, the greater should be the half-lives of both calcium pools. In this regard, it is interesting to note from Table 1 in their article that, for the synaptosome preparations used to test the control condition and the two experimental conditions in which field exposure has no effect, the greater the mean half-life of the rapidly released pool, the greater also is the mean half-life of the slowly released pool. The data which show that 16-Hz amplitude modulation of the 450-MHz field stimulates the mean half-life of the slow pool also show that the synaptosome preparations used has the greatest mean half-life for the rapid pool. Thus, some question exists as to how much the statistically insignificant, greater mean half-life for the rapid pool in these synaptosome preparations contributed to the statistically significant increase in the mean half-life for the slow pool.

Finally, it should be noted that greater experimental reproducibility would be expected by maintaining the calcium concentration at 0.2 nM during both the radiolabelling and perfusion periods. Data presented in Table 3 of the article show that a 0.2 nM concentration does not enhance calcium efflux. Use of calcium-free medium during the perfusion period alters the steady-state calcium fluxes established during the radiolabelling period. Since the completeness of the washing of the synaptosomes by the calcium-free medium is variable, this variability will affect the measurements of calcium efflux.

A third group of investigators studying calcium efflux from nervous tissue has conducted two studies (Merritt, Shelton, and Chamness 1982; Shelton and Merritt 1980) on the effects of pulse amplitude modulated microwave fields applied at various energy densities and specific absorption rates. They have conducted experiments in which rat-brain tissue is labelled with radioactive calcium, either under in vitro conditions or by intraventricular injection and then exposed to field radiation under in vitro conditions. They have also conducted experiments in which both the radiolabelling (by intraventricular injection) and field exposure occur under in vivo conditions. They do not find any radiation-induced effects on calcium efflux, as determined by

statistical analysis of reported raw data. These studies by Merritt and his coworkers employ carrier signals and amplitude-modulation parameters different from those employed by Adey, Blackman and their coworkers and, thus, do not directly address the significance of the positive findings by Adey and Blackman. The *in vitro* studies by Merritt and his colleagues suffer from the same experimental limitation of those by Adey and Blackman with chick-forebrain hemispheres: the brain tissue slices incubated under *in vitro* conditions are far too large to sustain adequate metabolism of the cell populations within each tissue slice. The experiments in which radiolabelling and field exposure occur under *in vivo* conditions, however, do not suffer from this limitation. They yielded negative findings.

A recent publication in this field is by Dutta et al. (1984) on the effects of the 915-MHz radiation, amplitude modulated at 16 Hz, on calcium efflux from cultured human neuroblastoma cells. Monolayer cultures are near-maximally radiolabelled by incubation in supplemented Minimum Essential Medium with ^{45}Ca for 1 h. Each culture is washed three times following the radiolabelling period, and the radioactivity initially present in the chase-incubation medium is determined. The cells are exposed to the field for 30 min at specific absorption rates ranging from 0.00 to 5 mW/g. Medium collected from exposed and control cultures after a 30-min chase incubation is centrifuged at 500 x g to remove cells or large debris and then counted for radioactivity. The results demonstrate that exposure to the microwave field at a SAR of 0.05 mW/g increases calcium efflux during the 30-min exposure period by roughly 50 percent.

In the Dutta et al. study (1984), selection of neuroblastoma cell cultures as the cellular material offers the advantages of (1) establishing large numbers of replicate samples for experimentation, (2) working with nervous tissue cells that can be maintained under optimum physiological conditions throughout the experiments, and (3) working with cells that can be consistently and effectively washed free of radiolabelling medium. The investigators provide cpm data and use these raw data for all statistical analysis (two-tailed Student's t-test). They conduct control experiments demonstrating no difference in calcium efflux from cells kept in an incubator from those kept inside the exposure chamber and sham exposed. They find that three SAR magnitudes are associated with a statistically significant increase

n calcium efflux; the SAR of 0.05 mW/g elicits the greatest increase. In all .hree instances where a positive effect is demonstrated, the mean cpm data for :he exposed cultures is greater than that for all exposure conditions in which :here is no increase. Moreover, in all three of these instances, there is no ıadir in mean cpm data for the companion control cultures.

In sum, we believe only two studies adequately demonstrate that exposure)f nervous tissue cellular material to amplitude-modulated microwave radiation increases calcium efflux. The study by Lin-Liu and Adey (1982) indicates that field exposure of synaptosomes increases the rate of efflux of a slowly released pool. The study by Dutta et al. (1984) is the best controlled of all <u>in vitro</u> studies. This latter study is the only study to report an increase in calcium efflux sufficient in magnitude to warrant further experimentation in order to characterize the mechanism responsible for the enhanced calcium efflux. Notice should be taken of the observation by Dutta et al. that the magnitude of the SAR may be the most important determinant of field exposure effects. Finally, it is probably not coincidental that the only two studies to show positive radiation effects use cellular material that can be radiolabelled, washed, and chase incubated more consistently than the material used in the earliest studies (i.e., forebrain hemispheres and brain-tissue slices). Although brain-tissue slices of any magnitude offer the advantage of working with histologically intact tissue, this advantage is severely handicapped by the inability to appropriately handle such slices throughout the course of the experiment.

It is now time for the investigators in the field of radiation biology to re-examine the worth of those reports arguing 10 to 20 increases in calcium efflux based upon data gathered from experiments with unusually large N values and suspect methods of statistical analysis. Such practices are not acceptable in other areas of cell-biology research, and they should not be acceptable in this area either. It is time for us to accept as valid, positive findings only those reports showing relatively large, radiation-induced effects from experiments with reasonable N values and statistical analyses conducted with raw laboratory data. It is time to initiate studies which show how variation in the parameters of field exposure vary the magnitude, as opposed to an on-versus-off nature, of the radiation-induced effects. And, it is time to begin investigations of whether

adiation-induced effects are associated with changes in cellular processes nat either regulate calcium metabolism and/or are regulated by calcium etabolism. For example, there is exciting new evidence that phosphoinositide etabolism regulates the transient increase in free, cytoplasmic calcium that ccurs in cell populations when stimulated with agents that use calcium as a econdary messenger (Berridge 1984). It is, thus, appropriate to ask if field xposure conditions which alter calcium efflux alter phosphoinositide etabolism similarly. It is only through the application of such standards nd expectations that the work in this field will begin to contribute to the ainstream of modern cell-biology research, and begin to establish the extent o which we should be concerned with the health effects of exposure to radio requency and microwave radiation.

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ıe mean value reported for the exposed group and the mean of the value for ıe sham exposed or control group. Finding a universal measure of the "normal ınge" for such a diverse collection of endpoints as reflected in the Tables ; not quite as straightforward. The best choice appears to be the standard eviation. Actually, when used with laboratory animals, the standard eviation is a very conservative estimate of the "normal" range for a ırticular biological quantity. Good experimental technique deliberately nimizes variability in order to increase the sensitivity of the tests. It ; quite possible that completely healthy, free-ranging animals would show ırger variations than caged, genetically uniform animals maintained on ıiform diets. However, the standard deviation serves our purpose if these ıalifications are factored into any decisions that might be based on the ılues given in the Tables. The "Magnitude" column in Tables II and III gives fraction in which the numerator is proportional to the difference between ıe means of exposed and control populations and the denominator is roportional to the standard deviation of the values observed.

For example, consider the entries in Table II under Rogers at 12 kV/m. xposure of hives to this field causes a reduction in hive weight (i.e., honey roduction) which is ten times the normal variations in this quantity from one ontrol hive to the next. This is clearly a large effect and one which would ave serious implications for beekeepers who chose to place their apiaries nder EHV transmission lines. In contrast, consider the last entry in Table I. Hamer (1968) reported that exposure of human subjects caused an increase f 2 ms in reaction time. However, the normal variability in reaction times or individual subjects from one test to the next was greater than 40 ms. egative results in studies by Bayer et al. (1977), de Lorge and Marr (1974), e Lorge and Grissett (1977), Johansson, Lundquist, and Scuba (1973), Rupilius 1976), and Schuy and Waibel (1979) cast serious doubt on the validity on amer's study. But if we assume that the effect is real, it would be small nd would have little "biological significance." As important as information bout magnitude is, a surprisingly large number of reports do not include this nformation.

It should be emphasized that almost all of the studies summarized in ables II and III have been subjected to statistical tests. It is customary hat investigators report effects only when they believe on the basis of

experimental conditions. The last column in Tables II and III, labelled "Independent Confirmation," indicate the status of the studies with regard to confirmation by independent investigators.

The electric field studies in Table II are listed in order of decreasing unperturbed air field strength which would be required to produce the reported effect. In this way, Table II facilitates decisions regarding the relevance of individual studies to the ELF antenna fields. In many of the studies, the reported electric fields were measured in aqueous media. For electric fields specified in the soil (e.g., near the antenna ground), the first column under "Minimum Field for Effect" applies directly. However, it is necessary to use field theory to determine the air field strength which would be necessary to induce the required field in the medium. Because the internal field strength in a conducting medium is very much smaller than the corresponding air field strength, gross errors could be made in interpreting studies relative to transmission line exposure if this fact is ignored.

In evaluating the health significance of a potential biological effect, it is important to have a measure of the magnitude of the effect. To give an example, after your last physical examination, your physician might have said, "Your red cell count is a little lower than the average, but it is well within the normal range. It probably doesn't cause you any problems and I wouldn't recommend any medication for the condition." Your physician can measure your hematocrit with very high accuracy--within a few per cent. S/he also knows the average value of the hematocrit for the population in general with very high accuracy since it has been measured and reported for millions of patients. But s/he also knows that there is a wide variation in hematocrit among people, none of whom have related clinical symptoms of illness. Hence, s/he can say accurately that your count is lower than the average but that you are still "normal." Therefore, in evaluating the significance of a reported effect one should certainly consider the qualitative nature of the effect, but also one should take into account how large the effect would be under realistic conditions of exposure.

The next to last column in Tables II and III have been added to help evaluate the magnitude of the effects which have been reported by the investigators after exposing subjects to electric and/or magnetic fields. The obvious measure of the magnitude of an effect is simply the difference between

laboratory studies which claim effects of extremely low frequency electric fields are summarized in Table II. Table III provides a comparable analysis of the claims of bioeffects from ELF magnetic fields. Many of these studies are subject to scientific criticism because of the experimental design or the analysis of the results. However, no attempt has been made to select or reject reports on the basis of scientific validity. The Tables include publications ranging from papers in referred scientific journals to preliminary laboratory reports. The Tables provide basic objective data from each of the papers. Beyond this, the reader will have to provide his or her own subjective values as to the qualitative nature of the claimed effects. But with the help of the tabular data, the evaluation of each of the studies should be greatly facilitated.

At this point, it would be very helpful if someone could tell us which of these claimed effects are real, which are simply chance events, and which are the result of poor experimental design or investigator bias. Certainly, appearance in a peer-reviewed journal is not a guarantee of validity. Most scientific journals would rather err on the side of publishing faulty research than to be responsible for suppressing ideas--particularly controversial ideas. Scientists are trained to look critically at any report. But there is no foolproof method for the evaluation of the validity of a particular scientific publication. If the experimental design is good, if the effects are large by comparison to the sample-to-sample variation and from one replicate of the experiment to another, and if there is a well-defined relationship between the magnitude of the field and the magnitude of the effect, a single report may be convincing. When any or all of these criteria are absent, a study must be received with reservation. For subtle effects, probably the best measure of validity will come from the confirmation of the findings by an independent laboratory. In practice, identical replicate experiments from one investigator are rarely attempted by other, independent laboratories. At best, we can only hope for closely related studies. From the scientific point of view, this is completely adequate. Our goal is to learn about biological effects in some generality. If replicate or similar experiments fail to confirm previously reported effects, it does not mean that the original investigator was wrong, but it does imply that the originally reported results, at best, must have been very subtly related to the

the negative" in any general sense. It is possible to rule out specific phenomena for certain conditions if they are understood mechanistically. But it would be philosophically as well as practically impossible to anticipate and test for all phenomena under all possible combinations of conditions.

Screening studies with negative results have relatively little scientific value. If the experiments are not guided by rational postulates and the results are negative, it may simply mean that the investigator was looking for the wrong endpoint under the wrong exposure conditions or perhaps that his or her methods were not sensitive enough to detect subtle effects which actually were present. For this reason, this report has made no attempt to catalogue negative studies. Many are listed in the References, especially if their results have bearing on the validity of studies which claim effects. Still, there is reassurance in the fact that the random searching, carried out by many investigators with many different species of experimental subjects and under conditions which in many cases exceeded exposures typical of the Navy's antenna, revealed no marked deleterious effects. This situation should be considered in light of the fact that for obvious reasons it is relatively difficult to publish negative screening studies in reputable journals. It is quite possible that many preliminary or small-scale investigations have never been revealed.

Finally, we should recognize that most investigators have a built-in, subtle bias toward finding results. It is neither personally nor scientifically rewarding to produce negative results over an extended period of time. A special tribute is due to those investigators who have taken the care to replicate their experiments before publication and who have exercised care and ingenuity in isolating artifacts which could have led to erroneous results.

POSITIVE CLAIMS

Of course, there are biological effects of electric fields. There are, in fact, biological effects which result from exposure to extra high voltage (EHV) transmission line fields under certain circumstances. However, there have been so many diverse claims of effects that scientists, regulatory agencies and the public have not only become interested but also concerned and confused. To assist in the evaluation of this large body of literature, the

subject. A large subset of the subjects consisted of utility employees who had worked in large electric and magnetic fields for periods up to two decades. A vast array of physiological, biochemical and psychophysical tests was performed on these subjects. Many of the endpoints studied were chosen because of claimed effects by other investigators. The program has been in progress for approximately one decade. Even though the exposure levels have been much larger than those associated with the Navy's proposed antenna, Professor Hauf and his colleagues have found no effects in their subjects which can be attributed to field exposure.

In a sense, the Battelle studies have been even more thorough. There are obvious limits to the exposure time and to the tests which can be performed on human subjects. However, the mice and rats in the Battelle program could be exposed for very long periods of time (up to four generations of mice) and could be sacrificed to study organ systems of interest. Far greater numbers of experimental animals were used than would have been possible with human experimentation with concomitantly greater statistical power in the results. Unperturbed 60-Hz electric fields of 100 kV/m were used in many of the tests. Large batteries of tests of behavior; hematology and serum chemistry; immunology; cardiovascular function; bone growth, structure, and healing; pathology; endocrinology; neurophysiology; neurochemistry; reproduction, growth, and development; and mutagenesis and teratology have been carried out. The most intensive part of the screening studies extended over the period from 1979 through 1982. Suggestions of a few possible effects which deserve further investigation have come from the Battelle program (see Table II). However, the program, taken as a whole, has been overwhelmingly negative.

Studies with human subjects are particularly valuable because, even if the results are negative, they are immediately applicable to the species in which we all have the greatest interest. Since the Hauf studies found no effects in blood chemistry, it is reasonably safe to conclude that there will be no blood chemistry effects on other human subjects exposed to 50-Hz, 20-kV/m electric fields. Note the words "reasonably safe to conclude" instead of "certain." It can always be argued that sick individuals, old persons, or children will respond differently than the subjects investigated. It is also reasonable to assume that there will be no effects on blood chemistry at 40 or 75 Hz as well as at lower field strengths. But it must be emphasized that we cannot "prove

challenge. Success depends not only on the concepts of experimental design but also on meticulous attention to detail during its execution.

The classic study by Tucker and Schmitt (1978) on the perception of magnetic fields by human subjects is a fascinating example of the problems and challenges of this work. These investigators set out to determine the ability of their subjects to detect the presence of 60-Hz magnetic fields in the range of 7 to 15 G. In the early stages of their work, they found a subgroup of subjects who consistently were able to determine when the field was on. Concerned that either tactile or auditory clues rather than the magnetic field might be responsible for the successes, the investigators began a heroic series of improvements in their experimental equipment to isolate the subjects from the coils which were the source of the magnetic field. In the end, not one of 200 subjects was able to detect the field. Less persistent and less skillful experimenters would have concluded that certain human beings had a special ability to perceive these fields. In reviewing the data in the Tables, it should be remembered that very few of these studies were given the careful design and multiple checks which characterized the Tucker and Schmitt investigation.

NEGATIVE STUDIES

The bulk of the screening experiments have been negative, i.e., the investigations failed to show effects which could be attributed to exposure to power-frequency fields. Of course, this is to be expected in screening studies. Many different endpoints are studied, not because effects are anticipated but, "just to be sure." The most thorough programs have been the most negative. There have been many extensive screening studies in laboratories throughout the world but two are outstanding for the breadth and depth of their undertakings: (1) the studies with small laboratory animals (principally mice and rats) at the Battelle Pacific Northwest Laboratory in Richland, Washington under the direction of Dr. Richard Phillips and (2) the studies with human subjects at the Forschungsstelle fur Elektropathologie in Freiburg, West Germany under the direction of Professor Rudolf Hauf.

In Professor Hauf's program, healthy subjects were exposed to 50-Hz electric fields up to 20 kV/m or magnetic fields up to 0.3 mT (3 G) for periods of 3 and 5 h, with control periods and replicate exposures on each

effects associated with ELF electric or magnetic fields. The basic role which epidemiology can play in the study of the fundamental question of possible biological effects of ELF electric and magnetic fields has been carried out. If we are to discover subtle effects, more sensitive experimental procedures will be required.

LABORATORY STUDIES

The second category of studies involves experiments performed under controlled conditions in the laboratory. In such studies, biological subjects who are exposed to carefully defined fields for known periods of time are compared to similar subjects which are treated--to the best of the investigator's ability--in exactly the same manner except for exposure to the field. When large numbers of subjects are used and appropriate statistical analyses are applied, it is possible--in principle--to detect differences between the exposed and the "control" or "sham exposed" populations that are even smaller than the normal variations occurring spontaneously in all living species. Thus, with skillful experimental design, laboratory studies are able to reveal subtle effects which would be missed in epidemiological studies or by casual observation.

Everything depends upon the quality of the experimental design. The most sophisticated statistical techniques can tell only what the odds are that two groups of subjects differ. Whether that difference results from field exposure or some other factor depends upon the skill and ingenuity of the experimental design. There are very few general principles to guide scientists. Experiments which require subjective evaluation of the biological endpoints (e.g., scoring "normal" and "abnormal" cells in a microscopic preparation) are particularly susceptible to unintentional investigator bias. To combat this tendency, biologists have devised a technique called "blind scoring." In this case, samples are coded before evaluation and, at the time of scoring, the investigator performing the evaluation does not know whether the samples have been exposed or not. To counter possible bias during the treatment phase of the studies, some experiments are performed "double blind," i.e., neither the investigators conducting the treatments nor the investigators scoring the endpoints knows the identity of the samples. Beyond a few such principles of experimental design, each experiment is its own

EPIDEMIOLOGY

The epidemiological studies take advantage of the fact that certain subjects are exposed to fields in the normal course of their daily activities. The epidemiologist compares the health of these subjects with others who have not been exposed. Since there is no direct control by the experimenter over the length or magnitude of the exposure or of other environmental influences to which these subjects have been exposed, this kind of survey is expected to reveal only large scale or unusual effects. The quality of an epidemiological study depends to a very large degree upon the skill and originality of the investigator(s) in selecting groups of subjects for comparison, and, after determining that there are statistically significant differences between groups, in devising methods to ascertain which of many possible environmental influences are responsible for those differences. Epidemiology has provided valuable clues in the search for the causes of disease. However, it is a difficult science and subject to many pitfalls. It is important to remember this particularly when the differences in the incidence of disease between groups in an epidemiological study are small.

An alphabetical listing of relevant epidemiological investigations is given in Table I. The experiences of the subjects in these surveys range from short exposures to extremely strong fields, such as by linemen carrying out maintenance procedures barehanded, to chronic exposures to comparatively weak fields in the home. Many of these study results were completely negative, i.e., the health of the exposed subjects was found to be normal. In others, there are suggestions of subjective complaints that are difficult to quantify. In fact, it was some of these claims reported in the early Soviet epidemiological surveys that sparked interest in the possible biological effects of transmission line fields. However, attempts in Canada, Sweden, Norway, West Germany, and the United States to confirm these findings have been unsuccessful. Although no single study has been thorough enough to be conclusive by itself, taken collectively, the body of epidemiological studies constitutes a very extensive, organized search for possible effects from exposure to ELF fields. If we recognize that this kind of investigation can only be expected to reveal large scale or unusual effects, it is apparent that the epidemiological approach has failed to detect any clearly defined health

that air electric fields as small as those of the proposed antenna will produce observable biological effects. Two of the characteristics which Langmuir found to be common to his examples of pathological science were: (1) the magnitude of the effect is substantially independent of the intensity of the cause, and (2) the effect is of a magnitude that remains close to the limit of detectability. As is evident from the survey which follows, these are uncomfortably accurate descriptors of most of the studies which report biological effects of small ELF electric and magnetic fields. This should put us on guard and stimulate our skepticism. We have had many years of optimistic searching for effects. Now it is time to ask ourselves what we know with reasonable certainty.

Finally, I would like to make an observation about the process by which important public policy decisions are made on subjects involving specialized technical knowledge. In a democratic society, final decisions are made by agencies or boards representing the people as a whole. For a highly specialized subject, these agencies must rely--at least in part--on the scientists who are active in the field of interest. It is important to realize that this consultative process has its problems. The scientists upon whom we must rely spend almost all of their professional careers seeking new knowledge. To be successful in this pursuit they must be original, innovative and speculative. After prolonged searching, the investigator may begin to believe in the existence of an effect--more as a matter of faith than from solid evidence or through an understanding of the mechanisms involved. This is understandable and, from the standpoint of basic science, even may be desirable. But when decisions of importance to society's progress must be made, we need reasonably solid facts. At this point we must ask the scientists to take a completely different approach to the subject and to separate what is really known from that which is speculative. Sometimes the borderline is fuzzy and we get equivocation or even speculation presented as fact.

In response to the Navy's request, I have prepared an objective, analytical summary of the world literature on biological effects of ELF electric and magnetic fields. The format of the summary should make it easier to determine the validity and relevance of the reports. From the standpoint of scientific evidence, these studies fall into two general categories: epidemiological studies and laboratory studies.

after prolonged exposure. In the absence of predicted effects, the bulk of this work has consisted of screening surveys which have been patterned after commonly performed toxicological studies. Subjects in these studies were exposed to large fields and tested for as many different physiological and psychological indicators of health as permitted within budgetary constraints. The choice of field strengths has been arbitrary. In many cases, the largest practical fields were used in the rationale that extreme exposures would increase the probability of revealing effects. In many cases, the biological endpoints studied simply reflected the individual investigators' biological or clinical interests. However, since many different investigators have contributed to the subject, many different endpoints have been observed. Screening investigations were essential in the early phase of the concern for possible effects of ELF fields. Some of this work continues today. However, the essential need for screening studies has been fulfilled. Few toxicological investigations have been so thorough and so negative.

Third, a surprisingly large portion of the relevant papers report only a single experiment. A single screening experiment provides guidance for the design of subsequent experiments but means little by itself. The pressure for publication is understandable, particularly if long periods of time are required to complete a single experiment. However, there should be no qualitative differences in the criteria for evaluating long- and short-term studies. Before placing reliance on any paper in this review, it is desirable to ask whether the reported effects have been seen repeatedly by the investigators.

We are all aware that chance and artifact can lead to observations that give the appearance of a real phenomenon. This is particularly likely to occur when studies are not guided by quantitative models and scientific postulates or where the desire for discovery supplants healthy, scientific skepticism. In the past, observations of this kind have led to fads in science. In a colloquium at the General Electric Research Laboratory about 30 years ago, Irving Langmuir (1953) described these digressions from reality as "pathological science." His examples included N-rays, mitogenic rays and extrasensory perception. In contrast with these examples, electric fields do exist and can be measured with precision. Without doubt, electric fields of sufficient magnitude do produce biological effects. However, it is not clear

STUDIES OF PLANTS AND ANIMALS EXPOSED TO ELF ELECTRIC AND MAGNETIC FIELDS

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INTRODUCTION

Over many years, numerous investigators have looked for the effects of a wide range of extremely low frequency (ELF) electric and magnetic fields on a variety of specimens. Much of this work has been carried out over the last decade and was motivated by a concern for possible effects from transmission line fields and the Navy's Seafarer antenna. The investigations have included very extensive surveys of almost every aspect of the health and functions of a wide variety of plants and animals, including human subjects, which were exposed in various ways to ELF fields. The goal of this review is to put this massive body of observations into a form which the reader can use in evaluating the potential for biological effects of ELF fields.

A few general introductory remarks about the subject matter and its information base are in order:

First, it is important to recognize that we are not considering the introduction of a new drug or food additive. There is nothing new or unusual about electric or magnetic fields. Life has evolved over the eons in the presence of these fields. In fact, our bodies are a maze of ELF electric fields that, in many cases, are larger than the fields which would be induced within our bodies by exposure to ambient air fields.

Second, only a small fraction of the work summarized here fits the pattern of classic, hypothesis-testing scientific research. This is because nothing in the firmly established knowledge of the interactions of tissues with electric or magnetic fields predicts biological effects from internal fields as small as those which result from exposure to the air fields of the proposed antenna. Although there are no obvious hazards associated with such exposures, many agencies have expended substantial resources to be sure that we have not overlooked some subtle effect or an effect which might appear only

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statistical tests that the odds are less than one in 20 that the results occurred purely by chance. The columns labeled "Magnitude" are intended to help evaluate the importance of an effect if it is assumed to be real and are not intended to provide a statistical test of validity. However, if one scans those studies conducted at fields less than 100 kV/m, an interesting generalization emerges. With very few exceptions, the magnitude ratio is less than unity. An electrical engineer might say that these effects were below the noise level.

As indicated above, the best test for validity of a subtle effect is independent confirmation in other laboratories. As time passes, more and more of these subtle effects have been so tested. Again and again, they fail to be observed in independent tests. Occasionally repeat experiments in the original laboratory are unsuccessful. H. B. Graves (Graves, Long, and Poznaniak 1979) has aptly characterized this as the "Cheshire Cat Phenomenon." Remember that we are dealing, by and large, with screening studies, not hypothesis-testing scientific experiments. Thus, there is no a priori guide indicating what results should be expected on a rational basis. Are these effects, which are pulled out of the biological noise by statistical techniques, real or are they fantasy? At the present time it is impossible to say for individual ex, .riments. However, it is apparent when the summary of the entire field is considered that we must approach those unconfirmed studies reporting subtle effects with reservation--neither ignoring them or their possible health implications nor accepting them as fact and making major technological decisions based on the findings.

When evaluating the possible effects of the air fields of the ELF antenna, it is important to note that there are no confirmed biological effects of electric fields in air less than 1 kV/m. When soil fields near the grounded end of the antenna are in the range 0.1 to 10 V/m, the situation is not as straightforward. This case must be evaluated more carefully for each potentially exposable biosystem.

There are no independently confirmed effects for ELF magnetic fields at field strengths less than about 10 mT (100 G). In the range 10 to 50 mT the confirmed effects (magnetophosphenes) appear to be the result of the magnetically induced electric fields in the subjects rather than a direct action of the magnetic field.

SUMMARY AND RECOMMENDATIONS

First, in the role of advisor to the Navy, it is important to give the best possible assessment of knowledge as it is available today. An analytical summary of the bioeffects literature fails to reveal any clear evidence for biological effects from exposure to air fields comparable in magnitude to those of the proposed antenna. In its 1977 review of this subject, the National Academy of Sciences' Committee on Biosphere Effects of Extremely-Low-Frequency Radiation noted the possibility of a shock from "step potentials" (i.e., contacts made between two points on the surface of the ground near the terminations of the antenna). A complete analysis of the question should consider, on a case by case basis, possible effects on soil and water organisms which are in the electric fields of the ground terminations of the antenna.

Second, as scientists interested in the interactions of living things with ELF electric and magnetic fields, what guidance can we find in the work which has been accomplished up to the present time? The rich collection of observations at our disposal today is, in part, the product of massive screening investigations carried out in many independent laboratories throughout the world. This phase of the work is complete. It has been essential but extremely inefficient. We are in a position now to proceed with this work with far greater efficiency. Two kinds of work are needed: confirmation studies and hypothesis-testing research.

The screening studies have bequeathed a large collection of unconfirmed "effects." The Tables contain a very long shopping list of experiments which should be repeated. In contrast to random searching which frequently entails a great deal of wasted effort, replication of these studies cannot fail to be useful if the work is performed skillfully. If the results are positive, we have a new basis for investigation of bioelectric phenomena; if the results are negative, it will help to clean up some of the debris which has accumulated from careless screening investigations and which, if allowed to stand unchallenged, may cause unnecessary concern.

Of course, hypothesis-testing has become the classic form of scientific research largely because of its inherent efficiency. Not only do the experiments elucidate the concepts under test, but entirely unexpected effects are more likely to be discovered when contrasted with the predictions of

carefully formulated postulates than are likely to be discovered through random searching or through studies where there is no preconceived quantitative prediction of what to expect.

TABLE I

EPIDEMIOLOGICAL STUDIES OF THE BIOLOGICAL
EFFECTS OF HIGH VOLTAGE TRANSMISSION LINES

A large number of epidemiological studies, which collectively have surveyed a bro d spectrum of health indicators, have sought to determine whether those subjects exposed to large 60-Hz fields have been affected by that experience. These studies differ qualitatively from laboratory experiments where the magnitudes of the fields and the exposure durations were defined. The experiences of the subjects range from short exposures to extremely large fields, such as by linemen carrying out maintenance procedures barehanded, to chronic exposures to comparatively weak fields by residents living near a high voltage transmission line right-of-way. Since there is no basis for quantitatively comparing exposures, the studies are listed alphabetically by senior author, with date of publication (Column 1). Column 2 describes the subject(s) of each study; Column 3 gives the health-related end point(s) studied; and Column 4 gives the result(s).

TABLE I
Epidemiological Studies of the Biological Effects of High Voltage Transmission Lines

Author	Subjects	End Points Studied	Results
Amstutz ('80)	Livestock on Farms with 765 kV Transmission Lines.	Extensive survey of health and productivity.	Negative.
Asanova ('66)	Substation and Transmission Line Workers.	Vascular tone, heat activity, peripheral blood properties, subjective effects.	Possible effects.
Bauchinger ('81)	Switchyard Workers.	Chromosome and sister chromatid exchange analyses; hematological, hormonal, and behavioral tests.	Negative.
Broadbent ('82)	Transmission and Distribution Workers.	General health.	Negative.
Broadbent ('85)	Power Transmission and Distribution Workers.	General health.	Negative.
Coleman ('83)	Male Leukemia Victims in Southeast England.	Incidence of leukemia.	Electrical workers in the report have 17% higher incidence of leukemia than for population as a whole.
Eckert ('76)	Human Infants.	Sudden infant death (SID).	Incidence of SID is reported to be greater in basements, first and second floors of residences than in higher locations.
Fole ('73,'74)	Substation Workers, Engineers.	Heart rate, subjective reactions.	Possible effects.

TABLE I Cont.
Epidemiological Studies of the Biological Effects
of High Voltage Transmission Lines

Author	Subjects	End Points Studied	Results
Fulton ('80)	Residents Near Power Lines.	Incidence of childhood leukemia.	Negative.
Glasgow ('81)	Population Near Transmission Lines.	Secondary accidents.	Negative.
Hauf ('81)	Switchyard Workers.	A very large battery of bio-chemical and physiological parameters.	Negative.
Hennichs ('82) Algers ('81)	Cows Exposed to 400 kV Trans-mission Line Fields.	Fertility.	Negative.
Hodges ('79)	Crops: Corn, Oats, Soybeans.	Overall productivity.	Negative.
Houk ('76)	Sanguine Personnel.	Comprehensive medical survey.	Negative.
Issel ('77) Kupfer ('77)	Linemen who work barehanded on 110-380 kV transmission lines.	Clinical tests and psychological exams.	Negative.
Knave ('78)	400 kV Switchyard Workers.	Chronic health effects, nervous system, cardiovascular system, blood, fertility.	Negative.
Kouwenhoven ('67) Singewald ('73)	EHV transmission line workers.	Comprehensive medical survey, neurology, urology, opthomology, blood, ECG, and EEG.	Negative.
Krivova ('68)	Substation and Transmission Line Workers.	Peripheral blood.	Possible effect.
Krumpe ('72)	Sanguine Personnel.	Comprehensive medical survey.	Negative.

TABLE I Cont.
Epidemiological Studies of the Biological Effects of High Voltage Transmission Lines

Author	Subjects	End Points Studied	Results
McDowall ('83)	Male Leukemia Victims in England and Wales.	Incidence of leukemia.	Conflicting results.
Milham ('82)	Male, Leukemia Victims in Washington State.	Incidence of leukemia.	A possible relationship between incidence of leukemia and occupations with exposure to electric and magnetic fields is suggested.
Morton ('82)	Women in Oregon.	Incidence of cancer.	Possible relationship of cancer to magnetic fields is discussed.
Nordenson ('84)	Switchyard Workers and Salesmen.	Chromosomes of lymphocytes.	Fivefold greater numbers of chromosome breaks in switchyard workers than salesmen.
Nordstrom ('78)	400 kV Switchyard Workers.	Preliminary study.	Birth defects and chromosome damage.
Nordstrom ('81)	130-400 kV Switchyard Workers.	Chronic health effects: Reproduction, chromosome damage.	Negative on all findings except 2.3% vs. 0.7% chromosome damage.
Nordstrom ('83)	Switchyard Workers.	Reproduction.	Possibly higher incidence of birth defects.
Perry ('81)	General Population.	*Incidence of suicide.*	A *relationship* between suicide rate and residential magnetic field is claimed.

TABLE I Cont.
Epidemiological Studies of the Biological Effects of High Voltage Transmission Lines

Author	Subjects	End Points Studied	Results
Peterson ('80)	Male Workers in California.	All deaths.	Electrical workers are less likely to die of leukemia than the population as a whole. (PMR=89)
Reichmanis ('79)	General Population.	Incidence of suicide.	"Inconclusive" (i.e., negative).
Roberge ('76)	EHV Maintenance Workers.	Broad health survey.	Negative.
Rogers ('80,'81)	Trees, Shrub, Pasture Vegetation, Crops, Wildlife, Honeybees near a 1100 kV Transmission Line (ground level fields up to 12 kV/m).	Growth, development and behavior.	Douglas fir trees within 18 m of the conductors displayed corona and reduction in growth in top three whorls of tree. Honeybees in 1 m hives at 12 kV/m (but not 7 kV/m) showed adverse effects. (See Table II). No other clear effects in deciduous trees, shrubs, pasture, crops, farm animals, or wildlife.
Sazonova ('67)	Substation Workers.	Memory, semimotor reactions, smell threshold, heart function.	Possible effects.
STCMPI,PRC ('79)	High Voltage Workers.	General Health.	Exposed subjects were statistically different than control subjects in high blood pressure,

TABLE I Cont.

Epidemiological Studies of the Biological Effects of High Voltage Transmission Lines

Author	Subjects	End Points Studied	Results
STCMPI,PRC ('79 cont.)			tremors of the face, abnormal ECG and vascular properties and cholesterol.
Stopps ('79)	Transmission Line Workers.	Broad health survey.	Negative.
Strumza ('70)	Residents along a High Voltage Transmission Line.	Medical and pharmacological records.	Negative.
Swerdlow ('83)	Adult Population of England and Wales.	Incidence of eye cancer.	In three of eight years, the incidence of eye cancer in electrical and electronics workers was statistically greater than for the general population.
Tomenius ('82)	Childhood Cancer Victims.	Incidence of childhood cancer.	Negative. Relationship between magnetic fields and cancer were mixed.
Tuhackova ('82)	Substation Workers.	Humoral regulation and general health.	Negative.
Vagero ('83)	Radio, TV and other Electronics Industry Workers Compared to Working Population as a Whole.	Incidence of cancer.	Relative risk for men: 1.15 ± 0.05; for women: 1.08 ± 0.07. Respiratory tumors in men: 1.5 ± 0.2. Authors do not feel that

TABLE I Cont.
Epidemiological Studies of the Biological Effects
of High Voltage Transmission Lines

Author	Subjects	End Points Studied	Results
Vagero ('83 cont.)			it is possible to identify causal agent but suggest that it may be airborne.
Ware ('74)	Cattle Under 765 kV Transmission Line.	Health and grazing habits.	Negative.
Wertheimer ('79, 80)	Childhood Cancer Victims.	Incidence of childhood cancer.	A relationship between incidence of cancer and residential magnetic field is claimed.
Wertheimer ('82)	Adult Cancer Victims.	Incidence of cancer.	A relationship between incidence of cancer and residential magnetic field is claimed.
Wright ('82)	Male Leukemia Victims in Los Angeles.	Incidence of leukemia.	Possibly higher incidence of leukemia in occupations with exposure to electric fields is suggested.

TABLE II

LABORATORY STUDIES OF THE EFFECTS OF ELF ELECTRIC FIELDS ON PLANTS AND ANIMALS

Table II presents studies of plants and animals exposed in the laboratory to ELF electric fields in a form such that they can be compared conveniently and meaningfully with the fields associated with the Navy's antenna. The range in the quality of the work represented here is extreme. In many cases the work is preliminary in nature. In some, even the authors are very cautious about interpreting their results as field-related effects.

This summary is intended principally to answer the questions: If the effects claimed in the study were real, (1) would they be expected to occur as a result of exposure to electric fields of the Navy's antenna, and (2) would the nature and magnitudes of the effects suggest a hazard?

Although this summary does not provide an intensive critical analysis of the literature, nevertheless it does provide some indication of the reliability of the research. In general, the papers are listed in order of the minimum field in air (before introducing the subject) which would be required to produce the effect claimed by the author, beginning with the highest electric fields and progressing to the lowest. The conclusions of many investigators have been negative, i.e., they claim no effects which can be related to electric fields; thus, these papers can not be included in Table II even though they may be useful in the overall evaluation of the health and safety issue.

<u>Column 1</u> gives the senior author and publication date of the paper.

<u>Column 2</u> describes the nature of the study and the effects claimed by the authors.

<u>Column 3</u> gives the frequency of the electric field at which the study was conducted. In a few investigations, repetitive pulses were used. In these instances, line spectra covering a wide range of frequencies were involved. Therefore, an estimate of the range of frequencies involved in the exposure is given.

<u>Column 4</u> gives the minimum unperturbed electric field at which the claimed effect occurred. In some cases, these values are an estimate of the fields. When the subject is introduced into the field, the

local fields near the subject may be much larger than the unperturbed field. Where the reference specifies a field in an aqueous medium, the corresponding field in air which would be necessary to produce the field used in the original experiment is computed using the principles of field theory. For many experiments, the ratio of the two fields is just the reciprocal of the ratio of the complex conductivities of the two media. If the fields in air exceed approximately 1000 kV/m, the actual value is of little importance since breakdown of the air will occur.

Column 5 gives an indication of the magnitude of the effect claimed in comparison with the normal biological variability in the observed end point. Where possible, this is expressed as the ratio of the magnitude of the effect attributed to the electric field (normally the difference between the means of exposed and control samples) to the standard deviations of the values observed. A positive or negative sign has been added in some cases to emphasize that the end point for the exposed population is larger or smaller respectively than the control population. Some of the reports are not quantitative. In others, the information necessary to calculate standard deviation is lacking. This information is not intended to tell whether a claimed effect has been validated in a statistical sense. Rather, it should be useful in an evaluation of potential hazards. It is an indication of the risks which we *might* run if, in fact, a particular biological effect is someday confirmed. When the magnitude of the observed effects in an unconfirmed report (the numerator of the fraction) is comparable to or much less than the normal biological variability (the denominator of the fraction), or when it does not appear to be correlated with the strength of the electric field, we naturally question whether is is a true effect of the field exposure.

Column 6 indicates whether the study has been confirmed by independent investigators. Confirmation is indicated by (+). If another investigator has attempted but failed to reproduce the effect or has reported the opposite effect, this is indicated by (-). Where no known attempt at confirmation has been made, the column shows (0).

Laboratory Studies of the Effects of ELF Electric Fields on Plants and Animals

Authors	The Study	Frequency	Minimum Field for Effect		Magnitude (Effect/) S.D.)	Independent Confirmation
			Medium	Air		
Jacob ('81)	Inactivation of Yeast Cells.	50 kHz (pulses)	1 MV/m	>>1000 kV/m		+
Hulsheger ('81)	Killing of *E. coli*.	pulses	700 kV/m	>>1000 kV/m		+
Nordenson ('84)	Chromosome Breaks in Human Lymphocytes Exposed in vitro.	3-μs pulse	350 kV/m	>>1000 kV/m	5/1	0
Sale ('67, '68) Hamilton ('67)	Lysis of Erythrocytes.	20-μs pulse	300 kV/m	>>1000 kV/m		+
Mild ('82)	Killing of Human Leucocytes in vitro.	1 MHz (pulses)	200 kV/m	>>1000 kV/m		+
Kinosita ('77)	Lysis of Erythrocytes in vitro.	50 kHz (pulses)	200 kV/m	>>1000 kV/m		+
Grover ('82)	Permeability Change in Lymphocytes.	20-μs pulse	200 kV/m	>>1000 kV/m		+
Hulsheger ('81, '83)	Killing of Microorganisms.	1-ms pulse	100 kV/m	>>1000 kV/m		+
Witt ('76)	Synthesis of ATP in Isolated Spinach Chloroplasts.	30 Hz (pulses)	100 kV/m	>>1000 kV/m		0
Ben-Sasson ('82)	Increased Membrane Permeability in Human Erythrocytes.	pulse	100 kV/m	>>1000 kV/m		+
Grover ('82)	Permeability Change in Red Blood Cell Membrane.	20-μs pulse	80 kV/m	>>1000 kV/m		0

Laboratory Studies of the Effects of ELF Electric Fields on Plants and Animals

Authors	The Study	Frequency	Minimum Field for Effect: Medium	Minimum Field for Effect: Air	Magnitude (Effect/S.D.)	Independent Confirmation
Teissie ('81a)	Transient Pores Produced in Phospholipid Vesicles.	>100 kHz	30 kV/m	>>1000 kV/m		+
Brower ('80)	Inhibition of Growth of Microasterias Cells.	1 Hz	1400 V/m	>>1000 kV/m		0
Teissie ('81b)	Activation of Na/K Transport System in Human Erythrocytes.	100-6000 Hz	1000 V/m	>>1000 kV/m		0
Serpersu ('83)	Increased Uptake of Rubidium by Human Red Blood Cells.	1 kHz	1000 V/m	>>1000 kV/m	5/1	0
Chen ('80) Sher ('63)	Electrophoresis of Human Red Blood Cells.	10 Hz	400 V/m	>>1000 kV/m		+
Marsh ('68)	Regeneration of Planaria. No effects were observed up to 200 V/m. Between 300 and 500 V/m, bipolars were produced. Above 500 V/m all of the organisms died.	60 Hz	300 V/m	>>1000 kV/m		0
Straub ('75)	Altered Membrane Potential in Isolated Frog Skin.	20 Hz	2 A/m^2 skin current	>>1000 kV/m		0
Rusyayev ('73)	Changes in Coagulation and Fibrinolytic Properties of Blood.	50-20,000 Hz	300 V/m	>>1000 kV/m		0
Friend ('75)	Deformation of Amoebae.	10-1000 Hz	300 V/m	>>1000 kV/m		+

Laboratory Studies of the Effects of ELF Electric
Fields on Plants and Animals

Authors	The Study	Frequency	Minimum Field for Effect: Medium	Minimum Field for Effect: Air	Magnitude (Effect/ S.D.)	Independent Confirmation
Dumansky ('77)	Ability to Concentrate, Blood Cholinesterase, and Glucose Affected in Human Subjects.	50 Hz		15 kV/m	7/9 concent. 20/9 choline 14/9 glucose	-
Gann ('76)	Dogs Subjected to Hemorrhage had More Rapid Heart Rate.	60 Hz		15 kV/m		
Kozyarin ('81)	Behavioral and Biochemical Changes in Rats.	50 Hz		15 kV/m	3/1 behavior -1/1 brain cholinesterase 2/1 liver glycogen	0
McKee ('78) Bankoske ('76) Johnson ('79)	*Leaf Tip Corona Damage.*	60 Hz		15 kV/m		+
Marino ('76a)	Three Generation Mouse Study. Third generation mice in vertical fields are smaller than controls. Third generation mice in horizontal fields are larger than controls.	60 Hz		15 kV/m	third generation males: -4/4 vertical +2/4 horizonal	-
Marino ('77)	Reduced Water Intake and Weight in Rats.	60 Hz		15 kV/m	-19/17 weight 4/2 albumen -9/3 hydroxy-corticosterone	+/- - -

TABLE [illegible] Cont.

Laboratory Studies of the Effects of ELF Electric Fields on Plants and Animals

Authors	The Study	Frequency	Minimum Field for Effect: Medium	Minimum Field for Effect: Air	Magnitude (Effect/) S.D.)	Independent Confirmation
Cerretelli ('79) Conti ('81)	Decreased Growth Rate in Rats. Changes in Blood Cells in Dogs and Rats.	50 Hz		25 kV/m	1/2 (body weight)	-
Graves ('78a) Hackman ('81)	Transient Increase in Cortico-sterone Levels in Mice.	60 Hz		25 kV/m	50/33	0
Hjeresen ('80)	Rats Prefer Field. Rats select field as opposed to no field space during light periods for fields from 25 to 50 kV/m.	60 Hz		25 kV/m	25/18 at 50 kV/m 14/18 at 25 kV/m	0
Altmann ('76)	Increased Metabolic Activity of Bees.	50 Hz		20 kV/m		0
Graves ('78a)	Transient Enhancement of Growth in Chicks.	60 Hz		20 kV/m	5/10	0
Mamontov ('71)	Cell Division in Mice. Mitotic index of certain cells increased.	50 Hz		20 kV/m	9/15 corneal epithelium 5/1 liver 2/4 kidney	0
Hodges ('[illegible])	Leaf Tip Corona in Corn.	60 Hz		16 kV/m		+
[illegible]	Decreased Accuracy of Work in [illegible] after 2-Hour [illegible]	50 Hz		16 kV/m		-

TABLE II Cont.
Laboratory Studies of the Effects of ELF Electric Fields on Plants and Animals

Authors	The Study	Frequency	Minimum Field for Effect		Magnitude (Effect/) S.D.)	Independent Confirmation
			Medium	Air		
Sazonova ('64)	Reduced Work Capacity of Rabbits. Rabbits were exposed to electric fields for 1 h before being tested for work capacity. No effects were observed until the experiments had been repeated over a period of about 23 days for 35-kV/m fields and about 18 days for 100-kV/m fields.	50 Hz		35 kV/m	30/30	0
Graves ('78b)	Perception of Field by Pigeons.	60 Hz		32 kV/m		+
Bootz ('78)	Egg Weight and Behavioral Effects in Chickens.	50 Hz		30 kV/m		0
Hjeresen ('82)	Swine Prefer to Remain out of Field.	60 Hz		30 kV/m	3/8	0
Itaku ('82)	Induced Current in Trees Becomes Nonlinear Because of Corona.	50 Hz		30 kV/m		0
Phillips ('76)	Perception of Field by Swine.	60 Hz		30 kV/m		0
Phillips ('81a)	Possible Effects on Swine. Fields may cause lower infant mortality, behavorial changes, poorer mating performance, and variable effects on fetal development (malformations).	60 Hz		30 kV/m		0

TABLE II Cont.
Laboratory Studies of the Effects of ELF Electric Fields on Plants and Animals

Authors	The Study	Frequency	Minimum Field for Effect		Magnitude (Effect/) S.D.)	Independent Confirmation
			Medium	Air		
Aoki ('82)	Decreased Germination and Root Growth of Raphanus sativus.	60 Hz		50 kV/m		0
Ehret ('81)	Increased Activity in Mice.	60 Hz		50 kV/m	8/3	+
Hopkins ('76)	Perception in Certain Specialized South American Fish.	60 Hz	0.003 V/m	50 kV/m		+
Le Bars ('76)	Increased Leucocyte Count in Rabbits, 8 h/day for 20 days.	50 Hz		50 kV/m		0
Le Bars ('78)	Increased Leucocyte Count and Blood Urea in Rats Exposed 100 days, 8 h/day.	50 Hz		50 kV/m		-
Le Loc'h ('75)	Possible Biochemical Changes in Rats and Rabbits.	50 Hz		50 kV/m		-
Phillips ('76)	Piloerection on Swine Ears.	60 Hz		50 kV/m		+
Rosenberg ('81)	Transient Increase in Activity in Mice on First Exposure to Field.	60 Hz		50 kV/m		+
Spittka ('69)	Drinking Behavior of Rats. Rate decreases in electric field.	50 Hz		50 kV/m	25/30	0
Drenkard ('83)	Behavioral Reaction in Cows.	60 Hz	1 mA	40 kV/m		+
Graves ('78a) Cooper ('81)	Decreased Activity of Chicks.	60 Hz		40 kV/m		0

TABLE II Cont.
Laboratory Studies of the Effects of ELF Electric Fields on Plants and Animals

Authors	The Study	Frequency	Minimum Field for Effect: Medium	Minimum Field for Effect: Air	Magnitude (Effect/) S.D.)	Independent Confirmation
Sander ('82) Bayer ('77)	Lower Leucocyte Count in Rats.	50 Hz		100 kV/m		-
Sieron ('82)	Increased Conductivity of Blood from Rats Exposed for 21 Days.	50 Hz		100 kV/m	3/2	0
Smith, LG ('81)	Delayed Dentition in Four Generations of Mice, Poorer Righting Reflex.	60 Hz		100 kV/m	2/7 teeth 1/4 righting	0
Watson ('75)	Increased Growth Rate in Cultured Chick Tibia.	10 Hz (0.1 s on, 0.9 s off)		100 kV/m	13/18	0
Seto ('83)	Growth Reduction in Rats Aged 4-8 Weeks.	60 Hz		80 kV/m	3/10	-
Walker ('82)	Increased Femur Length in Rats Conceived and Raised in Field.	60 Hz		80 kV/m	+3/4	-
Hjeresen ('80)	Rats Avoid Field.	60 Hz		75 kV/m	45-min. exp.: 1/2. Light half of 23.5-h exp.: 22/18 at 75 kV/m, 35/18 at 100 kV/m.	+
McCleave ('74)	Perception of Field by Fish.	75 Hz	0.007 V/m	70 kV/m	5/19	0
Gengerelli ('41)	Excitation of Frog Nerve in Air.	60 Hz		60 kV/m		0

TABLE II Cont.
Laboratory Studies of the Effects of ELF Electric Fields on Plants and Animals

Authors	The Study	Frequency	Minimum Field for Effect: Medium	Minimum Field for Effect: Air	Magnitude (Effect/) S.D.)	Independent Confirmation
Kanz ('51)	Threshold Changes for Taste, Smell, Hearing, and Touch in Human Subjects.	50 Hz		100 kV/m		0
Kuhne ('78)	Lower Leucocyte Count, Greater Activity in Rats.	50 Hz		100 kV/m		- leu. ct. + activity
Lefcourt ('81a,b)	Perception of Shock by Cows.	60 Hz	2.5 mA	100 kV/m		0
Malaguti ('80)	Increased Heart Rate in Dogs when Field is Turned on.	50 Hz		100 kV/m		0
Martin ('78)	Decreased Disuse Osteoporosis in Rats.	30 Hz		100 kV/m	8/9 mass 9/16 area	0
McClanahan ('83)	Decreased Fracture Stiffness in the Fibulae of Rats.	60 Hz		100 kV/m	-8/10	0
McElhaney ('68)	Rat Femur Studies. Many mechanical and chemical properties of bones were measured. No consistent pattern in effects is apparent. Non-malignant "tumors" reported but not confirmed by Martin ('78).	0, 3, 30 Hz		100 kV/m		0
Norton ('81)	Increased Cell Size and Adhesion to Glass in Cultured Bone Cells.	5-Hz square wave		100 kV/m		0

TABLE II Cont.
Laboratory Studies of the Effects of ELF Electric
Fields on Plants and Animals

Authors	The Study	Frequency	Minimum Field for Effect		Magnitude (Effect/) S.D.)	Independent Confirmation
			Medium	Air		
Rodan ('78)	Increased Incorporation of Thymidine in Cartilage Cells.	5 Hz		110 kV/m	2/1	0
Bassett ('68)	Increased DNA and Hydroxypro-line in Cultured Fibroblasts.	1 Hz		100 kV/m		0
Blanchi ('73)	Blood and ECG Changes in Mice. If there are effects, it is interesting that the results of 6-h and 1000-h exposures are essentially the same.	50 Hz		100 kV/m	14/12 lympho-cytes 12/12 neutro-phils 7/1 PR 1/12 QRS	-
Carmaciu ('77)	Increase of Antidiuretic Hormone and Decreased Diuresis in Rats.	50 Hz		100 kV/m	+4/4 diuresis	-
Free ('81)	Reduced Testosterone Levels in Rats Exposed for 120 Days.	60 Hz		100 kV/m	-6/10	0
Jaffe ('80)	Increase in Synaptic Excitabil-ity in Rats.	60 Hz		100 kV/m	1/2	0
Jaffe ('81)	Improved Recovery from Fatigue in Solius Muscles from Rats Exposed for 30 Days.	60 Hz		100 kV/m	1/3	0
Kalmijn ('74)	Feeding Response and Cardiac Deceleration in Rays.	60 Hz	0.0001 Vm	100 kV/m		+

TABLE II Cont.
Laboratory Studies of the Effects of ELF Electric Fields on Plants and Animals

Authors	The Study	Frequency	Minimum Field for Effect		Magnitude (Effect/) S.D.)	Independent Confirmation
			Medium	Air		
Solov'ev ('67)	Killing of Mice and Fruit Flies.	50, 500 Hz		400 kV/m		0
Watson ('83)	Paralysis of Flies.	50 Hz		400 kV/m		0
Drenkard ('83)	Prolactin and Corticosteroid Changes in Cows.	60 Hz	8 mA	300 kV/m		+
Norton ('79)	Increased Thymidine Uptake in Bone Cell Cultures.	5-Hz square wave		300 kV/m	1/1	0
Watson ('83)	Agitation of Flies.	50 Hz		300 kV/m		0
Tovmasjan ('76)	Depressed Immune Response in Mice Challenged with Sheep Erythrocytes.	50 Hz		250 kV/m		0
Fam ('80)	Decreased Food Consumption, Weight, and Hematological Values in Mice.	60 Hz		240 kV/m	15/10 weight	0
Peters ('72)	Perception in Catfish.	25 Hz	0.01 V/m	>200 kV/m		+
Knickerbocker ('67)	Smaller Second Generation Male Mice.	60 Hz		150 kV/m	3/5	-
Moore ('68)	Perception of Vibration by Skin of Human Subjects.	60 Hz	1 MV/m	150 kV/m		0
Hilmer ('70)	Aversion to Field Rats.	50 Hz		110 kV/m	8/10	+

TABLE II Cont.
Laboratory Studies of the Effects of ELF Electric
Fields on Plants and Animals

Authors	The Study	Frequency	Minimum Field for Effect: Medium	Minimum Field for Effect: Air	Magnitude (Effect/) S.D.)	Independent Confirmation
Billette ('81)	Contraction of Neck Muscles in Dogs.	60 Hz	7 mA	>1000 kV/m		0
Plum ('74)	Electroanesthesia and Electro-sleep. Possible induction of sleep by application of small currents through electrodes on scalp. Possible use of electric current applied through elec-trodes to the head together with drugs to maintain anesthesia.	10-1000 Hz		>1000 kV/m		+
Monet ('81)	Increased Calcium Uptake by Embryonic Chick Tibias.	1000 Hz		>1000 kV/m	2-14/10	0
Rodan ('81)	Reduced Alkaline Phosphatase in Cultured Bone Cells.	>1000 Hz	0.02 V/m	>1000 kV/m		0
Bassett ('74a,b)	Stiffness of Fracture Repair in Dog Bone Increased.	10^3-10^4 Hz pulse	2 V/m	1000 kV/m	7/3	0
Knickerbocker ('67)	Paralysis in Mice.	60 Hz		1000 kV/m		0
Gann ('74)	Killing of Tissue Culture Cells. Very clear effect at 600 kV/m but none at 200 kV/m.	60 Hz		600 kV/m		0
Norton ('77)	Reduced cAMP in Bones.	5-Hz square wave		400 kV/m	6/15	0

TABLE II Cont.
Laboratory Studies of the Effects of ELF Electric Fields on Plants and Animals

Authors	The Study	Frequency	Minimum Field for Effect: Medium	Minimum Field for Effect: Air	Magnitude (Effect/) S.D.)	Independent Confirmation
Wachtel ('79)	Firing Rate Changes in Pacemaker Cells of Marine Mollusk (Aplysia).	60 Hz	0.1 V/m	>>1000 kV/m	clear effects	0
Goodman ('76, '79, '84) Greenebaum ('79a,b,'82) Marron ('78)	Changes in Mitosis, Shuttle Streaming, and Respiration in Slime Mold. Intermitotic period and shuttle streaming reported to be increased by exposure. Mixed reports on respiration.	45, 60, 75 Hz	0.7 V/m	>1000 kV/m	4/3 period 9/5 respiration	0
Marron ('83)	Altered Partition Coefficients for Physarum Amoebae.	60 Hz	1 V/m +1 G	>1000 kV/m		0
Faytel'Berh-Blank ('73)	Increased Phosphorus Transport Across Synovial Membrane of Knee Joint of Cats. Sinusoidal and pulse modulated ELF currents produced small increases in end point.	40-150 Hz	5 V/m	>1000 kV/m		0
Kenner ('75)	Reduced Disuse Osteoporosis in Rabbit Hind Limbs.	5 Hz	1 V/m	>1000 kV/m		0
Achkasova ('78)	Physiological Changes in Bacteria.	0.1 Hz-20 kHz	0.4 V/m	>1000 kV/m		0
Luben ('82)	Inhibition of Parathyroid Hormone Response in Cultured Cells and Isolated Mouse Cranial Bones.	>1-MHz pulse rate 15, 72 Hz	0.1 V/m	>1000 kV/m		0

TABLE II Cont.
Laboratory Studies of the Effects of ELF Electric Fields on Plants and Animals

Authors	The Study	Frequency	Minimum Field for Effect		Magnitude (Effect/) S.D.)	Independent Confirmation
			Medium	Air		
Irwin ('74)	Stimulation of Enervated Frog Sartorius Muscle.	2-ms pulse (500 Hz)	15 V/m	>>1000 kV/m		+
Borrelli ('83)	Nerve-Muscle Stimulation in the Human Hand.	100 Hz	10 V/m	>>1000 kV/m		0
Coate ('70c)	Decreased Growth of Sunflower Seedlings.	45, 75 Hz + 1 G	10 V/m	>>1000 kV/m	1/1	0
Gonzalez ('80)	Increased Amino Acid Synthesis in Bacteria.	5-50 Hz	10 V/m	>>1000 kV/m		0
Adrian ('77, '79)	Electrophosphenes and Electrophonics in Man.	60 Hz	10 V/m	>1000 kV/m		+
Strope ('84)	Gradual Reduction in the Magnitude of the membrane Potential of Canine Kidney Cells in vitro Over a Period of Four Hours.	15 Hz	7 V/m	>>1000 kV/m		0
Smith ('79)	Dedifferentiation of Frog Erythrocytes.	50 Hz + DC	5 V/m	>>1000 kV/m		+
Straub ('72) Coate ('70b)	Sensitivity of Aquatic Animals.	100 Hz	4 V/m	>>1000 kV/m	clear effects	+
Vassilev ('82)	Alignment of Isolated Microtubules in Cells.	2-ms pulse at 10 Hz	2 V/m	>>1000 kV/m		0

TABLE II Cont.
Laboratory Studies of the Effects of ELF Electric Fields on Plants and Animals

Authors	The Study	Frequency	Minimum Field for Effect		Magnitude (Effect/) S.D.)	Independent Confirmation
			Medium	Air		
Galuszka ('69)	Immobilization of Honeybees.	50 Hz	20 mA	>>1000 kV/m		0
Montaigne ('84)	D.C. Offset in Vacuolar Potential of Characeae Cells.	250 Hz	100 V/m	>>1000 kV/m		0
Kraus ('72) Tager ('75) Lechner ('74)	Bone Healing. Clinical studies in which magnetic fields excited implanted pickup-coils with leads going to electrodes in the bone. Qualitative reports of accelerated bone fracture repair.	5-25 Hz	100 V/m	>>1000 kV/m		-
Irwin ('74)	Stimulation of Frog Cardiac Muscle.	2-ms pulse	75 V/m	>>1000 kV/m		+
Anderson ('51)	Migration of Slime Mold. Migration of P. polycephalum was inhibited along the direction of the field.	60 Hz	70 V/m	>>1000 kV/m		0
Gagliano ('77)	Orientation of Spinach Chloroplasts.	50 Hz	70 V/m	>>1000 kV/m		0
Kloss ('83)	Change in Rate of Isolated Frog Heart.	60 Hz	60 V/m	>>1000 kV/m		0
Richez ('72)	Osteogenesis in Rabbit Humerus.	1 Hz	50 V/m	>>1000 kV/m		0
Pilla ('74)	Dedifferentiation of Amphibian Erythrocytes. Red cells change shape and nuclear morphology.	$100\text{-}10^4$ Hz	50 V/m	>>1000 kV/m		+

TABLE II Cont.
Laboratory Studies of the Effects of ELF Electric
Fields on Plants and Animals

Authors	The Study	Frequency	Minimum Field for Effect: Medium	Minimum Field for Effect: Air	Magnitude (Effect/) S.D.)	Independent Confirmation
Mortimer ('80)	Muscle Damage in Cats	>1000 Hz	200 V/m	>>1000 kV/m		0
Levy ('74)	Increased Fracture Healing in Dogs.	pulse	200 V/m	>>1000 kV/m		0
Miller ('79, '80a,b,'83) Robertson ('81a,b)	Decreased Growth Rate in Pea Roots.	60 Hz	200 V/m	>>1000 kV/m	8/5 at 400 V/m	0
Novak ('73)	Orientation of Algal Eggs. Rhizoids of developing *Fucus* eggs orient along the direction of the electric field.	2-200 Hz modified square wave	200 V/m	>>1000 kV/m		0
Riesen ('71)	Brain Organelles--Loss of Respiratory Control.	60 Hz	155 V/m	>>1000 kV/m	large effects	0
Potts ('70)	Electrically Evoked Response of Rat Eye.	500 Hz	100 V/m	>>1000 kV/m		0
Hassler ('77, '78)	Enhanced Bone Healing in Rabbits.	60 Hz	100 V/m	>>1000 kV/m	only two animals at 60 hz.	0
Norton ('77)	Modified Growth of Rat Calavaria in Culture.	5-Hz Half wave rectified	700 V(?)	>>1000 kV/m		0
Sheller ('82)	Contraction of Lung Tissues.	0.5-ms pulses	(?)	>>1000 kV/m		0

TABLE II Cont.
Laboratory Studies of the Effects of ELF Electric Fields on Plants and Animals

Authors	The Study	Frequency	Minimum Field for Effect		Magnitude (Effect/) S.D.)	Independent Confirmation
			Medium	Air		
Shandala ('79)	Blood Chemistry and Behavioral Changes in Rats. Exposures were intermittant for period up to 4 months.	50 Hz		15 kV/m		-
Tomashevskaya ('81)	Metabolic Changes in Rats.	50 Hz		15 kV/m		0
Tuhackova ('82)	Changed Hormonal Parameters in Human Subjects.	50 Hz		15 kV/m		0
Hansson ('81a,b)	Lower Weight Gain, Brain Cell Changes in Rabbits.	50 Hz		14 kV/m	7/2 weight	-
Gabovich ('78)	Changes in Metal Concentrations in the Tissues of Rats.	50 Hz		12 kV/m	2/1 Cu 1/1 Mo	0
Rogers ('80)	Lower Honey Production and Brood Growth in Bees.	60 Hz		12 kV/m	-50/5 hive wt. -6/12 wax +75/14 propolis.	+
Rogers ('81)	Increased Mortality in Bees.	60 Hz		12 kV/m	130/13	+/-
Cabanes ('81)	Detection of Fields by Human Subjects with Hands over Head.	50 Hz		11 kV/m		+
Dumansky ('79)	Reduction in Human Skin Temperature.	50 Hz		10 kV/m		-
Mild ('82)	Possible Highly Localized Cell Damage During Transient Shocks.			10 kV/m		0

TABLE II Cont.
Laboratory Studies of the Effects of ELF Electric Fields on Plants and Animals

Authors	The Study	Frequency	Minimum Field for Effect		Magnitude (Effect/) S.D.)	Independent Confirmation
			Medium	Air		
Kalyada (n.d.)	Transient Decrease in Heart Rate and Skin Temperature in Human Subjects.	50 Hz		10 kV/m		-
Lymangrover ('83)	Increased Corticosterone Production by Isolated Rat Adrenal Glands.	60 Hz		10 kV/m	1/1	0
Phillips ('76)	Transient Grounding in Swine.	60 Hz		10 kV/m		0
Sander ('82)	Avoidance of Field by Rats.	50 Hz		10 kV/m		+
Sommer ('64)	Hearing Electric Fields.	80 Hz	100 kV/m	10 kV/m		0
Warnke ('75)	Behavior Changes in Bees.	50 Hz		10 kV/m		+
Epstein ('76)	Increased Glucose Concentration in Erythrocytes in vitro.	60 Hz		9.6 kV/m		0
Lee ('81a,b)	Lower Production of Honey and Increased Propolization by Bees.	60 Hz	.	8 kV/m		+
Rogers ('81)	Lower Bee Hive Weight.	60 Hz		8 kV/m	5/4	+
Husing ('60)	Activity of Bees. Increases irritability and abandonment of hive.	50 Hz		8 kV/m		+
Deno ('78)	Perception of Hair Stimulation by Erect Male Human Subjects	60 Hz		7 kV/m		+

TABLE II Cont.
Laboratory Studies of the Effects of ELF Electric Fields on Plants and Animals

Authors	The Study	Frequency	Minimum Field for Effect: Medium	Minimum Field for Effect: Air	Magnitude (Effect/) S.D.)	Independent Confirmation
Deno ('78 cont.)	with Hand Held Above the Head. Note: with hands at side 50% perception occurs at fields of 20 kV/m. Thresholds for annoyance are 6 to 10 times greater than for perception.					
Greenberg ('78, '79,'81a,c)	Lower Honey Production by Worker Bees. Transient increases in hive temperature. Propolization of hives.	60 Hz		7 kV/m	-30/4 honey 3/2 propolization	+
Kozyarin ('77)	Hematological Effects in Rats.	50 Hz		7 kV/m		-
Andriyenko ('77a)	Impairment of Reproductive Ability of Rats after Four Months of Continuous Exposure.	60 Hz		5 kV/m		-
Andriyenko ('77b)	Reduction of Viable Sperm in Rats.	50 Hz		5 kV/m		0
Fischer ('78)	Norepinephrine Levels in Rat Brain. Increases reported after 15 min and decreases after 10 days.	50 Hz		5 kV/m	6/18 15 min.	0
Gann ('76)	Irritability in Baboons.	60 Hz		5 kV/m		-
Gillis ('78)	Hair Vibration in Mammals.	60 Hz		5 kV/m		+

TABLE II Cont.
Laboratory Studies of the Effects of ELF Electric Fields on Plants and Animals

Authors	The Study	Frequency	Minimum Field for Effect: Medium	Minimum Field for Effect: Air	Magnitude (Effect/) S.D.)	Independent Confirmation
Greenberg ('81b)	Reduced Hive Weight and Foraging Rate.	60 Hz		5 kV/m	3/2 foraging rate	0
Marino ('79a,b)	Decreased Rate of Fracture Healing in Rats.	60 Hz		5 kV/m	-13/6 healing index	0
Marino ('80b)	Blood Changes in Mice. "Animals respond to change in electrical environment not to the electric field itself."	60 Hz		5 kV/m	4/6 RBC 5/8 Htc	0
Marino ('83c)	Decreased Germination in Sunflower Seeds.	60 Hz		5 kV/m	4/3	0
Prokhvatilo ('76)	Inhibition and Delay in Iodine Uptake in the Thyroid Glands of Rats.	50 Hz		5 kV/m		0
Stampfer ('79)	Lower Red Blood Cell Count in Mice.	50 Hz		5 kV/m		-
Stern ('83)	Detection of Field by Rats.	60 Hz		5 kV/m		0
Bridges ('79a) Jenkins ('78) Zalewski ('75)	Predictions of Cardiac Pacemaker Reversion.	60 Hz		4 kV/m		0
Waibel ('75)	Heart Rate Decrease in Human Subjects. Very small (about 4%), very brief (20 s) decrease in	50 Hz		4 kV/m		-

TABLE II Cont.
Laboratory Studies of the Effects of ELF Electric
Fields on Plants and Animals

Authors	The Study	Frequency	Minimum Field for Effect: Medium	Minimum Field for Effect: Air	Magnitude (Effect/) S.D.)	Independent Confirmation
Waibel ('75 cont.)	heart rate reported for short (3-min) exposure.					
Altmann ('74a)	Feeding and Nesting Behavior of Mice. Animals prefer fields for drinking and play and no field space for nesting.	10-Hz square wave		3.5 kV/m		0
Giarola ('74)	Small Changes in Growth of Chickens.	45, 60 Hz		3.5 kV/m		-
Lang ('71,'72)	Water-Electrolyte Balance in Mice. This and the following experiment were designed to show that a shielded room with artifical field added (3.5 kV/m, 10-Hz square wave) is equivalent to normal conditions and different than no field. They claim to have demonstrated this.	10-Hz square wave		3.5 kV/m		0
Marino ('80a)	Increased Mortality in Mice.	60 Hz		3.5 kV/m		-
Butrous ('83a,b)	Inhibition and Abnormal Pacing of Implanted Cardiac Pacemakers.	50 Hz		3 kV/m		+
Kubsinskiy ('78)	Changes in Coagulative Properties of the Blood of Rats.	1000 Hz		3 kV/m		-

TABLE II Cont.
Laboratory Studies of the Effects of ELF Electric
Fields on Plants and Animals

Authors	The Study	Frequency	Minimum Field for Effect		Magnitude (Effect/) S.D.)	Independent Confirmation
			Medium	Air		
Tagaki ('71)	Perception of Transient Shock When Contacting an Umbrella. Minor associated response of heart rate and skin resistance.	50 Hz		3 kV/m		+
Wellenstein ('73)	Activity of Bees. Increased activity and swarming tendency.	50 Hz		3 kV/m		+
Bisping ('77)	Altered Performance of Implanted Cardiac Pacemakers.	50 Hz		2 kV/m		+
Moss ('84)	Altered Performance of Implanted Cardiac Pacemakers.	60 Hz		2 kV/m		+
Rogers ('82)	Decreased Weight of Honey Bee Hives.	60 Hz		2 kV/m	57/22 11 kV/m 41/22 6 kV/m 21/22 2 kV/m	+ + +
Krueger ('75b)	Decreased Fecundity of Chickens.	60 Hz		1.6 kV/m	-14/14	-
Deno ('78)	Perception of Neural Stimulation from Thumb Contact with an Umbrella. Annoyance is experienced by half of the subjects at about 5 kV/m.			1.5 kV/m (Median Field)		+
Zahner ('64)	Subtle Effects on Activity of Hamsters.	50 Hz		1.5 kV/m		0

TABLE II Cont.
Laboratory Studies of the Effects of ELF Electric
Fields on Plants and Animals

Authors	The Study	Frequency	Minimum Field for Effect: Medium	Minimum Field for Effect: Air	Magnitude (Effect/) S.D.)	Independent Confirmation
Dumansky ('76) Prokhvatilo ('76)	Decrease in Cholinesterase Activity and Level of SH Groups in Blood and Endocrine Activity in Laboratory Animals.	50 Hz		1 kV/m		-
Dumansky ('82)	Adverse Effects on Reproductive Function in Rats.	60 Hz		1 kV/m		0
Moos ('64)	Activity of Mice.	60 Hz		1 kV/m		0
Yes'kov ('79)	Increased Activity and Hive Temperature for Honey Bees.	100-1000 Hz		1 kV/m		0
Schua ('53)	Hamsters Move Nests out of the Field.			900 V/m		-
Altmann ('74b)	Blood Changes in Guinea Pigs. This study purports to show that absence of a field affects the blood of guinea pigs, but that 240 V/m is equivalent to normal conditions.	10-Hz square wave		240 V/m		0
Senatra ('78)	Decreased Sedimentation Rate of Human Blood.	1.6 kHz		240 V/m	-1/2	0
Dowse ('82)	Lengthened and Shifted Circadian Cycle of Activity in Fruit Flies after Shift in Time of Day for Application of Field.	10 Hz		150 V/m	2/3	0

TABLE II Cont.
Laboratory Studies of the Effects of ELF Electric Fields on Plants and Animals

Authors	The Study	Frequency	Minimum Field for Effect		Magnitude (Effect/) S.D.)	Independent Confirmation
			Medium	Air		
Knudsen ('74)	Detection of Fields by Certain Electroreceptive Fish.	60 Hz	0.00005 V/m	100 V/m		0
Fischer ('76)	Decreased Heart Rate in Rats.	50 Hz		50 V/m	20/80	-
Coate ('70a)	Mutations of Fruit Flies.	45, 75 Hz		20 V/m		-
Medici ('75)	Response Times in Monkeys. No effect at highest field strengths. Animals sensitive to either 7 or 75 Hz but not 60 Hz.	7, 45, 75 Hz		1-100 V/m	1/10 1 V/m 3/10 10 V/m 4/10 56 V/m	-
Anselm ('77)	Improved Driving Performance in Human Subjects.	10-Hz square wave		15 V/m	misc. driving errors: -5/7 unstable subjects +2/9 stable subjects speeding and touching edge of road: -2/14 unstable -3/100 stable	0
Bawin ('76)	Decreased Calcium Efflux from Excised Samples of Chick and Cat Brain. No effects were observed at 32 or 75 Hz. Response was not monotonically dependent upon field strength. No effects at 100 V/m.	6, 16 Hz		10 V/m 56 V/m (cat)	1/1	0

TABLE II Cont.
Laboratory Studies of the Effects of ELF Electric Fields on Plants and Animals

Authors	The Study	Frequency	Minimum Field for Effect		Magnitude (Effect/) S.D.)	Independent Confirmation
			Medium	Air		
Durfee ('75)	Growth of Cultured Tissue. Growth is reported to be inhibited in 60-Hz fields and accelerated in 75-Hz fields.	60, 75 Hz		10 V/m	10 V/m, 60 Hz: -4/1 fibroblast -2/1 kidney 10 V/m, 75 Hz: +3/1 fibroblast +6/1 kidney	0
Gribble ('75)	Changes in Circadian Physiological Properties of Rats.	45 Hz		5 V/m		0
Konig ('74)	Human Reaction Time. Type I fields (10 Hz) decrease reaction time. Type II fields (3-6 Hz) increase reaction time.	3-10 Hz		(?)		-
Kirmaier ('78)	Improved Driving Performance.	10 Hz		3 V/m	-17/50 dexterity errors	0
Graue ('74)	Orientation of Homing Pigeons. Homing pigeons were studied in Sanguine fields.	45, 75 Hz		<3V/m	10/85	0
Southern ('75)	Orientation of Gull Chicks. In Sanguine fields gull chicks move in a different direction than normal.	45, 75 Hz		<3 V/m	38/103	0

TABLE II Cont.
Laboratory Studies of the Effects of ELF Electric Fields on Plants and Animals

Authors	The Study	Frequency	Minimum Field for Effect: Medium	Minimum Field for Effect: Air	Magnitude (Effect/) S.D.)	Independent Confirmation
Blackman ('82)	Increased Calcium Efflux from Isolated Chick Brain.	16 Hz		2 V/m	1/2	0
Wever ('74)	Human Circadian Rhythms. Presence of an electric field is claimed to hold an isolated subject closer to a 24-h cycle than in absence of electric fields.	10 Hz		2 V/m	1/1	0
Noval ('76)	Weight and Hormonal Changes in Rats.	45 Hz		0.1 V/m	-10/3 weight	-
					-3/2 choline acetyl transferase	0
					+1/1 liver pyrrolase	0
					+3/4 corticosterone	-
Larkin ('77) Williams ('77)	Migrating Birds Show Temporary Course Changes in Response to Changes in Seafarer Antenna.	75 Hz		0.07 V/m 0.005 G	0	
Hamer ('68)	Human Reaction Time Effects. Reaction times were greater at low frequency than at high frequency.	2-12 Hz		0.04-4 V/m	2/46	-

TABLE III

LABORATORY STUDIES OF THE BIOLOGICAL EFFECTS
OF ELF MAGNETIC FIELDS

Table III presents studies of plants and animals exposed in the laboratory to ELF magnetic fields in a form such that they can be compared conveniently and meaningfully with the fields associated with the Navy's antenna. The range in the quality of the work represented here is extreme. In many cases the work is preliminary in nature. In some, even the authors are very cautious about interpreting their results as field-related effects.

Although this summary does not provide an intensive critical analysis of the literature, nevertheless it does provide some indication of the reliability of the research. In general, the papers are listed in order of the minimum field at which the effect was reported to have occurred, beginning with the highest magnetic fields and progressing to the lowest. The conclusions of many investigators have been negative, i.e., they claim no effects which can be related to magnetic fields; thus, these reports can not be included in Table III even though they may be useful in the overall evaluation of the health and safety issue.

Column 1 gives the senior author and publication date of the paper.

Column 2 describes the nature of the study and the effects claimed by the authors.

Column 3 gives the frequency of the magnetic field at which the study was conducted. In a few investigations, repetitive pulses were used. In these instances, line spectra covering a wide range of frequencies were involved. Therefore, an estimate of the range of frequencies involved in the exposure is given.

Column 4 gives the minimum magnetic field at which the claimed effect occurred.

Column 5 gives an indication of the magnitude of the effect claimed in comparison with the normal biological variability in the observed end point. Where possible, this is expressed as the ratio of the magnitude of the effect attributed to the magnetic field (normally the difference between the means of

TABLE III Cont.

exposed and control samples) to the standard deviations of the values observed. Some of the reports are not quantitative. In others, the information necessary to calculate standard deviation is lacking. This information is not intended to tell whether a claimed effect has been validated in a statistical sense. Rather, it should be useful in an evaluation of potential hazards. It is an indication of the risks which we might run if, in fact, a particular biological effect is someday confirmed. When the magnitude of the observed effects in an unconfirmed report (the numerator of the fraction) is comparable to or much less than the normal biological variability (the denominator of the fraction), or when it does not appear to be correlated with the strength of the magnetic field, we naturally question whether it is a true effect of the field exposure.

Column 6 indicates whether the study has been confirmed by independent investigators. Confirmation is indicated by (+). If another investigator has attempted but failed to reproduce the effect or has reported the opposite effect, this is indicated by (-). Where no known attempt at confirmation has been made, the column shows (0).

TABLE III

Laboratory Studies of the Biological Effects of ELF Magnetic Fields

Authors	The Study	Frequency	Minimum Field for Effect (mTesla)	Magnitude (Effect/S.D.)	Independent Confirmation
Irwin ('70)	Stimulation of Frog Muscle.	100 Hz	1000		+
Kolin ('59, '68)	Excitation of Frog Nerve and Muscle.	60 Hz	600		+
Shchelkunova ('70)	Decreased (10) Respiration Rate in *E. coli*.	1 Hz (pulsed)	500		0
Strzhizhovshii ('77)	Reduced Mitotic Index of Corneal Epithelial Cells of Mice Exposed in vivo.	1/30 Hz	300		0
Borrelli ('83)	Nerve-Muscle Excitation in the Human Hand.	100 Hz	200	clear effect	+
Chizhov ('75)	Killing of *E. coli.*	50 Hz	150		0
Lenzi ('40)	Decreased Takes of Treated Adenocarcinoma Inoccula in Mice.	42 Hz	150		0
Fam ('61)	Lower Weight Gain and Increased Water Consumption in Mice.	60 Hz	110	-3/2 weight 1/1 water	0
Druz ('66)	Variable Ability of the Isolated Tissues of Rats to Absorb Water.	50 Hz	100		0
Barlow ('47)	Magnetophosphenes in Human Subjects.	60 Hz	50		+
Lovsund ('79)	Stimulation of Frog Retinal Ganglion Cells.	20 Hz	50	clear effects	0

TABLE III cont.

Laboratory Studies of the Biological Effects
of ELF Magnetic Fields

Authors	The Study	Frequency	Minimum Field for Effect (mTesla)	Magnitude (Effect/S.D.)	Independent Confirmation
Caldwell ('68)	Immobilization of Honeybees.	60 Hz	30		0
Frank, ('83)	Increased Stiffness and Failure Strength in Rabbit Ligaments Exposed 7 h/day, 5 days/week for 21 days.	1 Hz	25	13/5	0
Lovsund ('81)	Response of Frog Retinal Cells.	20-30 Hz	20		0
Odintsov ('65)	Decreased Resistance to Viral Infection in Mice.	50 Hz	20		0
Polson ('82)	Stimulation of Nerves in Human Subjects.	180-μs pulse	20		+
Sakharova ('77)	Hormonal and Histological Changes in Rats	50 Hz	20		0
Sebestik ('74)	Decreased Thermal Stability in Erythrocytes from Mice.		20	1/1	0
Seidel ('68a,b)	Magnetophosphenes in Human Subjects.	20-40 Hz	20	clear effects	+
Soldatova ('82)	Morphological Changes in Rat Brain.	50 Hz	20		0
Udintsev ('74)	Elevated Hydroxycorticosteroids in Rats.	50 Hz	20		0
Udintsev ('78a)	Variable Effects on Thyroid Function in Rats.	50 Hz	20		0

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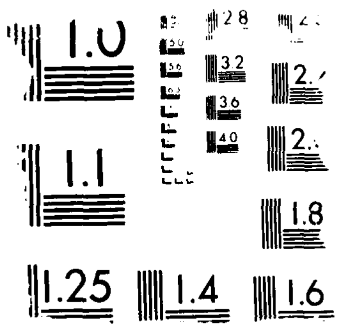
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TABLE III Cont.
Laboratory Studies of the Biological Effects
of ELF Magnetic Fields

Authors	The Study	Frequency	Minimum Field for Effect (mTesla)	Magnitude (Effect/S.D.)	Independent Confirmation
Udintsev ('78b)	Metabolic Changes in Testicular Tissues of Rats.	50 Hz	20		0
Udintsev ('79)	Altered Uptake of Iodine and Thyroxin in Rat Tissues.	50 Hz	20	1/1	0
Udintsev ('81)	Neuroendocrine Changes in Rats.	50 Hz	20		0
Tarakhovsky ('71)	Physiological Function Changes in Rats.	50 Hz	13		0
Assailly ('81)	Increased Calcium Uptake in Cultured Chick Tibia.	>1 MHz	10	3/5	0
de la Warr ('67)	Reduction in Cholesterol in Human Subjects.	?	10	44/25	0
Dernov ('68)	Peripheral Blood Changes and Morphological Damage in Rabbits.	50 Hz	10		0
Jolley ('83)	Decreased Calcium Efflux and Insulin Secretion in Isolated Rabbit Islets of Langerhans.	>1 MHz (pulsed)	10		0
Lovsund ('80a,b)	Magnetophosphenes in Human Subjects.	10-50 Hz	10	clear effects	+
Mitbreyt ('81)	Enhanced Bone Healing and Peripheral Circulation in Rats.	50 Hz	10		0
Moore ('79)	Acceleration and Inhibition of Growth of Bacteria and Yeast.	0-0.3 Hz	10		0

TABLE III Cont.
Laboratory Studies of the Biological Effects
of ELF Magnetic Fields

Authors	The Study	Frequency	Minimum Field for Effect (mTesla)	Magnitude (Effect/S.D.)	Independent Confirmation
Ossenkopp ('72a)	Physiological Maturation and Behavior in Rats Exposed in utero.	0.5 Hz	10	-2/1 -1/1	0
Chernysheva ('75)	Decreased Glycogen in Liver and Increased Glycogen in Heart of Rats.	50 Hz	9		0
Akoev ('76)	Perception by Skates.	<1 Hz	7		0
van der Kuij ('78)	Reduced Resorption of Bone at Tooth Extraction Sites in Dogs.	500 Hz	7	1/2	0
Tabrah ('78)	Reduced Growth and Respiration in Tetrahymena.	6 Hz	6		0
Batkin ('78)	Decreased Respiration in Mouse Tissue.	60 Hz	5		0
Sander ('82)	Lactate Level in Human Subjects.	5 Hz	5	3/8	0
Persinger ('70)	Lower Frequency of Lever Pressing in Adult Rats Which had been Exposed in utero.	0.5 Hz	3		0
Russo ('71)	Variable Avoidance Response in Honeybees.	60 Hz	3		0
Clarke ('79)	Detection of Field by Chickens.	60 Hz	2	4/3	0
Colacicco ('83a)	Increased Uptake of Calcium by Embryonal Chick Tibia in vitro.	>5000 Hz (pulses)	2		0

TABLE III Cont.
Laboratory Studies of the Biological Effects of ELF Magnetic Fields

Authors	The Study	Frequency	Minimum Field for Effect (mTesla)	Magnitude (Effect/S.D.)	Independent Confirmation
Eisenbach ('83)	Increased Motility and Reduced Chemotaxis in *E. coli.*	25-μs pulse 3 pps	2	7/2	0
Goodman ('83)	Accelerated RNA Synthesis in Isolated Salivary-Gland Chromosomes of *Sciara*.	>1000 Hz	2		0
Luben ('82)	Inhibition of Parathyroid Hormone Response in Cells and Isolated Mouse Cranial Bones.	>1-MHz pulse rate 15, 72 Hz	2	2/1	0
Persinger ('73)	Entrainment of Failing Rat Heart by a Rotating Magnetic Field.	0.5 Hz	2		0
Pilla ('81)	Increased Na Efflux from Erythrocytes in vitro.	200-μs pulse	2		0
Ramon ('81)	Decreased Survival of *E. coli.*	60 Hz	2		0
Sisken ('81)	Increased Generation of Isolated Chick Ganglia.	200-μs pulse	2	1/1	0
Smith ('77)	Increased Activity in Mice.	60 Hz	2		0
Smith, SD ('81)	Perturbation of Regeneration of Newt Limbs.	200-μs pulse	2		0
Smith, SD ('82)	Reduced Spleen Size in Mice Inoculated with Tumor Cells.	>100 kHz	2	1/1	0
Batkin ('77)	Slowed Tumor Growth in Mice.	60 Hz	1		0

TABLE III Cont.
Laboratory Studies of the Biological Effects
of ELF Magnetic Fields

Authors	The Study	Frequency	Minimum Field for Effect (mTesla)	Magnitude (Effect/S.D.)	Independent Confirmation
Mantle ('83)	"Relaxation" in Human Subjects.	5 Hz	1	1/7	0
Ossenkopp ('72c)	Increased Ambulation and Defecation in Ducklings Exposured During Incubation.	0.5 Hz	1		0
Persinger ('72a)	Activity in Rats.	0.5 Hz	1	1/1	0
Ramirez ('83)	Fruit Flies Avoid Field for Egg Laying.	50 Hz	1	2/3	0
	Increased deaths among eggs laid and held for 48 h in field.			2/1	0
Schmitt ('76)	Increased Alkaline Phosphatase Activity in Children Immobilized for Fracture Therapy.	50 Hz	1	7/12	0
Schober ('82)	Decreased Liver Sodium after 1-Day Exposure in Mice.	10 Hz	1	1/3	0
Dixey ('82)	Increased Release of Noradrenaline from Cultured Nerve Cells.	500 Hz	0.9	1/1	0
Aarholt ('81)	Decreased Generation Time in <u>E. coli.</u>	17 Hz 50 Hz	0.8 5.0	6/1 6/1	0
Brown ('78)	Modified Firing Rates of Electric Field Receptors in Skates.	1 Hz	0.5		+
Friedman ('67)	Increased Reaction Time in Human Subjects.	0.2 Hz	0.5		-

TABLE III Cont.
Laboratory Studies of the Biological Effects of ELF Magnetic Fields

Authors	The Study	Frequency	Minimum Field for Effect (mTesla)	Magnitude (Effect/S.D.)	Independent Confirmation
Ossenkopp ('72b)	Increased Thyroid and Testicle Weight in Rats Exposed in utero to Rotating Fields.	0.5 Hz	0.3	+5/2 thyroid 1/1 testicle	0
Persinger ('69)	Decreased Activity and Increased Defecation in Rats Exposed in utero to Rotating Fields.	0.5 Hz	0.3	1/1 activity 1/2 feces	0
Persinger ('72c)	Variable Effects on Organ Weight of Rats Rats Exposed in utero to Rotating Fields.	0.5 Hz	0.3	-1/3 thyroid wt. 2/1 testicle	0
Aarholt ('82)	Decreased and Increased Synthesis of Beta-Galactosidase in *E. coli*.	50 Hz	0.3		0
Greenebaum ('79a,b)	Changes in Mitosis, Shuttle Streaming, and Respiration in Slime Mold.	75 Hz	0.2	5/4 period 4/3 respiration	0
Greenebaum ('82)	Lengthened Mitotic Cycle in *Physarum*.	75 Hz	0.2	1/1	0
Gribble ('75)	Circadian Changes of Physiological Parameters in Rats.	45 Hz	0.2		0
Jenkins ('78)	Reversion to Fixed Rate, Implanted Cardiac Pacemakers.	60 Hz	0.2		+
Kavaliers ('84)	Inhibition of Nocturnal Morphine Induced Latency in Response to Heat Stimulus in Mice.	0.5 Hz	0.1-9	1/1	0
Beischer ('73)	Increased Serum Triglycerides in Human Subjects.	45 Hz	0.1		-

TABLE III Cont.
Laboratory Studies of the Biological Effects
of ELF Magnetic Fields

Authors	The Study	Frequency	Minimum Field for Effect (mTesla)	Magnitude (Effect/S.D.)	Independent Confirmation
Milburn ('71)	Certain Human Subjects Appeared to Perceive Magnetic Fields.	400-4000 Hz	0.1		-
Papi ('83)	Initial Orientation of Homing Pigeons Changed After Exposure for Periods up to 4 h.	0.03-0.06 Hz	0.06		0
Liboff ('84)	Increased DNA Synthesis in Cultured Cells.	15-4000 Hz	0.05	1/1	0
Christel ('81)	Increased Rate of Repair of Radial Osteotomies in Rats.	20-μs pulse	0.02		0
Delgado ('82)	Abnormalities in Chicken Embryos.	1-μs pulse	0.001	7/4	-
Ubeda ('83)	Abnormalities in Chicken Embryos.	0.5-μs pulse	0.001		-
Ludwig ('77)	Modified Skin Resistance in Human Subjects.		0.0001	5/9	0
Ehrman ('76)	Therapy for Headache, Rheumatic Illness, Circulatory Disorders, and a Variety of Subjective Illnesses.	0.004 Hz	0.00004		0
Achkasova ('78)	Physiological Changes in Bacteria.	0.5 Hz	0.000001		0

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ELECTROMAGNETIC INFLUENCES ON BIRDS

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INTRODUCTION

In 1977 the National Academy of Sciences (NAS) reviewed the evidence for biological effects of extremely low frequency (ELF) non-ionizing electromagnetic radiation (i.e., 1 to 300 Hz) on the behavior of migrating birds. The NAS Committee on Biosphere Effects of ELF Radiation recommended "further research on the basic biology of bird navigation and orientation designed to verify recent highly suggestive experiments." Since that review, the major conclusions of the NAS report still hold: electromagnetic sensitivity is well-established in birds. The review that follows examines critically several research papers on electromagnetic influences on avian migratory orientation and homing published primarily since the 1977 NAS Report. The primary emphasis is on the effects of magnetic fields although the effects of 60-Hz electric fields will also be examined. Additional information on the influences of geomagnetism on bird orientation and homing can be found in several recent reviews (Able 1980; Gould 1982, 1984; Keeton 1979a, 1979b; Lednor 1982; Moore 1980; and Walcott 1982). Wallraff (1983) has provided a particularly critical and useful review of geomagnetic effects on pigeon homing.

ELF STUDIES

During the early and middle 1970s, research on the biological effects of ELF fields at the U.S. Navy's Wisconsin Test Facility (Projects Sanguine and Seafarer) demonstrated that the electromagnetic fields generated by such large scale transmitting systems disrupt the orientation of birds. When Ring-billed Gull (Larus delawarensis) chicks were tested in a circular arena on clear days in a normal geomagnetic field they showed headings significantly clustered about a predicted bearing corresponding to the direction of migration (Southern 1975). When a large antenna buried one meter below the surface of

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the ground was energized, the headings of the gull chicks showed no clustering and were distributed randomly. Southern concluded that magnetic fields associated with such conditions may be sufficient to confuse orienting birds. In a related study, radar tracking of individual migrating birds flying over the same large alternating current (AC) antenna showed that the birds turned and changed altitude more frequently when the transmitting antenna system was operating than when it was not (Larkin and Sutherland 1977). These findings suggest that during nocturnal migratory flight, birds can sense low-intensity AC electromagnetic fields and that the sensitivity to an AC field may be much greater than the sensitivity required to detect the earth's direct current (DC) magnetic field. Williams and Williams (1978), using a small marine surveillance radar to detect migrating birds, also found that the operation of the Wisconsin Test Facility affected the direction taken by birds during their migratory flights, thus supporting the finding that migratory birds can sense the AC electromagnetic field produced by the transmitter.

The potential impact of ELF fields on migrating birds has been reviewed by Grissett (1980), and he concludes that the impact is minimal. However, Grissett relies heavily on the report of Williams and Williams (1978), and it should be pointed out that the small, low-power marine radar (3 kw, X-band) that the Williams' used in their study could not detect the majority of migrants flying over the antenna system because they were probably above the radar's maximum range of 300 meters. Furthermore, the marine radar they used could not distinguish minor changes in azimuth from altitudinal changes (Larkin 1984).

The recent work of Beaver, Asher, and Hill (1984) and Larkin (1984) is designed to assess the influence of electromagnetic fields associated with the U.S. Navy's ELF Communications System in the Upper Peninsula of Michigan on breeding and migrating birds. Beaver and coworkers (1984) are examining the ELF field effects on the parental and nesting behavior, fecundity, growth, and maturation of Tree Swallows (Tachycineta bicolor). As of 1983, only baseline data had been gathered with no data gathered in the presence of ELF radiation. In the Larkin (1984) study, migrating birds are being monitored with a trailer-mounted tracking radar located about 500 meters from a segment of the ELF antenna right-of-way. As of the fall of 1983, over 700 tracks of migrating birds had been recorded. These data are being gathered to document

the normal migration patterns over the Upper Peninsula of Michigan prior to ELF antenna construction and operation.

MAGNETIC INFLUENCES

Since the initial ELF field studies at the Wisconsin Test Facility, a growing body of behavioral evidence has been accumulated supporting the contention that birds are influenced strongly by magnetic field perturbation. Two lines of evidence have developed: field observations of flight behavior during magnetic storms, and studies of the orientation of migrants caged in altered magnetic fields.

Flight Behavior During Magnetic Storms

Magnetic "storms" are fluctuations in the earth's magnetic field that follow solar flares and other disturbances associated with sun spots. Such storms may range in intensity up to 3,000 gamma although most are less than 300 gamma (the total field strength is normally 0.5 G or 50,000 gamma); the storms obliterate the usual circadian pattern of 10 to 100 gamma fluctuations in field strength. The intensity of the storms is measured by a K index of magnetic activity. K values range from zero for magnetic disturbances of 0 to 4 gamma to 9 K for disturbances of 500 gamma and above. Keeton, Larkin, and Windsor (1974) found a correlation between normal fluctuations of the earth's magnetic field and the day-to-day variation in initial bearings chosen by homing pigeons (Columba livia) released repeatedly at a single test site under sunny skies. Because the magnetic fluctuations were less than 70 gamma (K <5), the authors conclude that the sensitivity of pigeons to magnetic stimuli is of the same magnitude as that demonstrated for honeybees. A later study by Larkin and Keeton (1976) showed that bar magnets mask the effect of the K fluctuations suggesting that the magnetic events themselves influence the orientation of normal homing pigeons. Moreover, the bar magnets, like natural magnetic disturbances, deflect a bird's bearing to the left. Magnetic storms not only affect the initial orientation of pigeons at release sites, the speed of homing appears to be influenced as well. Schreiber and Rossi (1976, 1978) found that speed of homing was negatively correlated with solar activity and hence magnetic storms. Similar results have been published by Carr, Switzer, and Hollander (1982).

Most of the studies of free-flying migrants report little or no influence of magnetic storms on flight directions (Able 1974; Richardson 1974, 1976) or flight speed (Larkin and Thompson 1980), but Moore (1977) found that K values were positively correlated with increased angular deviation of flight directions and that the mean flight direction tended to shift to the left on nights with magnetic storm activity.

Primacy of Magnetic Compass

Several recent studies have shown that the earth's magnetic field is used as a reference for the development of a migratory direction in birds (Alerstam and Hogstedt 1983; Beck and Wiltschko 1982; Wiltschko 1982; Wiltschko and Gwinner 1974; and Wiltschko, Gwinner, and Wiltschko 1980). Young Garden Warblers (Sylvia borin) hand-raised without ever seeing the sky were able to find their normal migratory direction when tested in the local geomagnetic field without visual cues (Wiltschko and Gwinner 1974). In later experiments it was shown that the non-visual orientation system can mature completely without seeing the sun and the stars (Wiltschko, Gwinner, and Wiltschko 1980). Similar tests with hand-raised Pied Flycatchers (Ficedula hypoleuca) and Savannah Sparrows (Passerculus sandwichensis) clearly indicate that the magnetic compass develops without input from celestial cues and that migratory direction is genetically encoded relative to the magnetic field (Beck and Wiltschko 1982; Bingman 1981). In a recent study, Alerstam and Hogstedt (1983) shifted the geomagnetic field at Pied Flycatcher nest boxes during the incubation and nestling periods. The field was shifted by Helmholtz coils mounted at the nest boxes. When the birds showed migratory restlessness two months later, a corresponding shift in the migratory orientation was observed. This study lends additional support to the magnetic calibration hypothesis and suggests that imprinting-like learning of celestial cues used in migratory orientation takes place at an early age. Unlike the findings of Wiltschko and Wiltschko (1975, 1976) that migratory birds frequently recalibrate their celestial compass against the magnetic compass, the results of Alerstam and Hogstedt (1983) show a long-lasting effect of magnetic calibration.

Wiltschko, Nohr, and Wiltschko (1981) showed that homing pigeons that had never seen the sun before noon could not use the sun compass in the morning

hours, however they were able to orient homeward. When these birds carried magnets they were disoriented, indicating perhaps they were using a type of magnetic compass. The results of this study suggest that homing pigeons can use a magnetic compass whether or not the sun compass has been established. The data also support the notion that the magnetic compass is the first source of compass information.

In an attempt to test whether the sun compass of homing pigeons is calibrated by the magnetic field, young pigeons were raised in an altered magnetic field in which magnetic north was turned clockwise about 65° in the 1974 and 1975 experiments and about 120° in 1980 experiment (Wiltschko et al. 1983). The pigeons could see the sun only in an abnormal relation to the magnetic field, and they were exercised only when the sky was totally overcast. On first flights in sunshine, homeward bearings of these experimental birds deviated clockwise from the mean of the bearings of control birds, but the deviation was only about half of what was expected. On subsequent flights in sunshine, the differences in orientation between experimental and control birds disappeared. These findings suggest a magnetic influence on learning the sun compass, but as Wiltschko et al. (1983) comment, the relationship between the two systems is more complex than that proposed by the calibration hypothesis.

Artificial Magnetic Fields

Artificial magnetic fields can influence the homing behavior of pigeons released from unfamiliar sites even under sunny skies. Visalberghi and Alleva (1979) performed tests by securing cylindrical magnets (in sunny conditions) and Helmholtz coils (under both sunny and overcast conditions) to the pigeons' heads. The latter units had either north (Nup) or south (Sup) poles up. Under overcast conditions, a distinct disorientation of Nups was recorded, and in sunny conditions, Nup and Sup birds showed greater scattering in vanishing bearings compared with control birds.

In a study designed to examine the roles of olfaction and magnetism in pigeon homing, Wallraff and Foa (1982) attached magnets to the head, neck, and wings of the anosmic and intact experimental birds and brass bars to the anosmic and intact controls. Although they found that olfaction is an integral part of the pigeons' navigational mechanism, the geomagnetic field

also plays a role. They suggest that magnetic information may explain the rudimentary homeward orientation in anosmic pigeons.

A similar study by Papi, Maffei, and Ioale (1983), just using magnets and brasses showed no differences in orientation or homing performance in four test releases performed from the four cardinal directions 20 to 27 km from the loft. In the same paper, Papi and his coworkers report on a second experiment that attempted to replicate the earlier studies of Walcott and Green (1974) and Visalberghi and Alleva (1979). Birds were equipped with Helmholtz coils connected to a battery. The polarity and intensity (±0.4 G) of the induced field oscillated in a roughly sinusoidal way with a frequency of 0.15 Hz. Controls wore identical coils without current and dummies of the other equipment. When released from 40 to 50 km North, South, and East of the loft, vanishing bearings of experimentals were more scattered than those of controls. In addition, controls homed faster. In most cases, however, differences between experimentals and controls were not significant.

The homing behavior of pigeons following 0.75 to 4 h exposure to an alternating magnetic field has been examined by Papi, Meschini, and Baldaccini (1983). They found that in most cases initial orientation under the sun was disturbed (decrease in homeward directedness) and, in two experiments, disturbance also occurred under overcast skies. The disturbance lagged behind treatment for some hours, and the degree of disturbance was in part related to the length of treatment. Despite the disturbance, homing performance was not affected.

Magnetic Anomalies

It is perhaps not surprising that naturally occurring magnetic anomalies in the earth's crust influence the homing behavior of pigeons. Experiments by Walcott (1978, 1980, 1982) show that homing pigeons are disoriented when released at magnetic anomalies and the disorientation is positively correlated with the strength of the anomaly. Similar findings have been reported from Switzerland by Frei (1982) and from southwestern Germany by Kiepenheuer (1982). Frei suggests that within the anomaly, the pigeons systematically respond to local directions of magnetic gradients, but Kiepenheuer doubts that flying birds would be able to do so in such a situation.

Magnetic Receptor

Although considerable evidence supports the influence of the magnetic field on direction finding in birds, the reception mechanism has not been explained. Several studies have documented the presence of magnetite crystals in birds. Walcott, Gould, and Kirschvink (1979) found localized concentrations of magnetite crystals in the heads of pigeons. The deposits were located in bone cavities near the midline of the skull, roughly between the olfactory bulb and the optic chiasma. Another study (Presti and Pettigrew 1980) has reported magnetite located in the neck muscles of pigeons and migratory White-crowned Sparrows (Zonotrichia leucophrys). However, Walcott and Walcott (1982) attempted to replicate these studies, and after examining over 80 pigeons, were unable to find the inducible remanence previously reported even though exactly the same techniques and equipment were used as in the earlier studies.

The Bobolink (Dolichonyx oryzivorous), a long distance transequitorial migrant, has recently been shown to respond to changes in the earth's magnetic field (Beason and Nichols 1984). In an attempt to locate the magnetic receptor, these authors discovered deposits of iron oxide (probably magnetite) in sheaths of tissues around the olfactory nerve and bulb, between the eyes, and also in bristles which project into the nasal cavity (Kirschvink and Gould 1981; Yorke 1979, 1981), but evidence coupling the magnetite to the magnetic sensitivity is lacking. Thus, the mechanism of perception of the magnetic field by birds is unknown.

Although much of this review has concentrated on magnetism and the orientation and homing of birds, the underlying mechanisms remain unknown. Moreover, in much of this work there is a serious problem with consistent replication (Thomson 1983) and at least one qualified skeptic wonders if "...it is possible that birds have no useful sensitivity to the earth's magnetic field" (Griffin 1982).

ELECTRIC FIELD EFFECTS

The biological effects of extremely low frequency electromagnetic fields has been summarized in an edited volume by Phillips et al. (1979), and the biological effects of high voltage AC transmission lines has been reviewed by Sheppard (1983). In both of these works there is a paucity of referenced

studies that deal with electric field effects on birds. Few documented biological effects have been attributed to transmission line electric fields, magnetic fields, or both (Lee, Bracken, and Rogers 1979). The authors speculate that if a bird approaches near an energized conductor, the field strength could be strong enough to cause mechanical vibration of feathers. However, to date no study has examined the behavioral responses of free-flying birds to high intensity 60-Hz electric fields.

Very few laboratory studies of the detection and behavioral responses of birds to 60-Hz electric fields have been conducted (Cooper et al. 1981; Graves 1981; Graves, Long, and Poznaniak 1979). In these studies, a conditioned suppression paradigm was used to determine whether pigeons could detect 60-Hz electric fields of 25 kV/m or 50 kV/m. Pigeons apparently can detect the field calculated to be greater than 10.5 kV/m but less than 21 kV/m at head level.

Even though pigeons are able to detect AC electric fields under laboratory conditions, noise parameters or exposure grid vibrations are potential artifacts associated with ELF field generation systems. Graves (1981) addressed this problem and studied electric field detection by pigeons which were either shielded by a Faraday cage or unshielded. Pigeons shielded from the ELF field did not show conditioned suppression while those unshielded did. Thus, pigeons are actually detecting the electric field and not the noise or vibration associated with the exposure system. Although definitive data are lacking, Graves and his coworkers suspect "that ELF effects can be explained by stimulation of peripheral receptor system and increased general arousal."

SUMMARY AND CONCLUSIONS

This review has attempted to cover the most important literature on the subject of electromagnetic field effects on birds. Two points have been emphasized: (a) the detection of magnetic fields and (b) the detection of electrical fields. Most of the work on magnetic fields relates to DC fields, and much more work is needed on AC field effects. There can be little doubt that many birds perceive DC magnetic fields, but the utility of this information to the bird is in doubt according to one authority. Geomagnetism may be used in direction finding, but the geomagnetic effect is like the

Cheshire Cat encountered by Alice in Wonderland: it has "the disconcerting habit of appearing without warning and then vanishing, in part or in whole, only to reappear at some later time" (Graves, Long, and Poznaniak 1979). At present, there is--more or less--agreement that geomagnetism probably functions as a compass, but there is serious disagreement as to whether geomagnetism functions as a map for navigation. Additional work will undoubtedly clarify the role of geomagnetism in the orientation and homing of birds and other animals.

Clearly more work needs to be done on the detection of and responses to AC electric fields by birds. Although laboratory work has started, field studies near transmission lines would be very valuable. If birds prove to be generally sensitive to electrical and magnetic fields, then this knowledge would be of greater benefit in assessing the ecological impact of systems that generate and transmit ELF radiation.

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cases where exposure to weak ELF-EMF fail to induce a bioeffect. In these cases, it is appropriate to question whether applying a somewhat different wave form or frequency might not have induced an effect.

Based on current evidence. one can conclude that weak fields can affect and alter various cell function(s). All effects are subtle except those observed at field strengths that would physically damage the cells. By subtle we mean that the cell's normal functions are not halted or, as far as can be seen, irreversibly disrupted; removal of the field generally allows an altered parameter to return to "normal." It is unclear from these experiments what effect such changes at the cellular level would have on a multi-celled organism with self-regulating capabilities or even on the long-term survival of a single celled organism. Therefore, whether these alterations represent a hazard or not cannot be ascertained on the data currently available.

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intensity (Miller et al. 1980). The investigators calculate that a 60-Hz, 450-V/m electric field will alter the membrane potential by 3 to 8 mv. It is noteworthy that membrane potential changes on the same magnitude have been obtained by other investigators studying the bio-effects of ELF-EMF exposure (Teissie and Tsong 1981).

SUMMARY

Despite the fact that the literature contains numerous, often disparate reports on the effects of weak electromagnetic fields (ELF-EMF), certain types of bioeffects appear to be emerging. In particular, there is increasing experimental evidence that cation fluxes are sensitive to ELF-EMF perturbation. In view of the secondary messenger role of Ca^{++}, as well as the homeostatic function of both Ca^{++} and Na^{+}, any perturbations in these functions could portend important physiological implications. At this time, the available data will not permit one to extrapolate whether a cell would show altered cation fluxes at the field intensities actually encountered in the vicinity of a power line or a communication's antenna. It does suggest, however, that additional experiments--preferably with greater sensitivity than those performed heretofore--be performed at low field intensities to address this question.

Associated with the evidence for altered cation flux, one also finds increasing evidence that the plasma membrane may be one of the primary interaction sites between weak ELF-EMFs and the cell. If this can be substantiated in the future, then it will be possible to move toward developing a model to explain the mechanism of interaction between weak fields and cells. The development of a working model will also allow one to extrapolate from the lab to the potential hazards of these fields with a greater degree of confidence.

ELF EMF electric and magnetic fields seem to produce similar bioeffects. It is unclear from the data available to date, whether magnetic effects occur through the induction of an extremely weak electric field in the cell or through another mechanism still to be defined. It is also unclear whether there is a synergism between the two types of fields. An important aspect that has emerged from the bioeffects literature is the presence of wave form dependence and frequency windows. This aspect is especially important in

Chiabrera, Grattarola, and Viviani (1984) have published a theoretical treatise that proposes a possible interaction mechanism between an applied electric field, ligands, and surface effectors. They propose that the E-field induces a microelectrophoretic effect that influences the distance between charged ligands and receptors and, in effect, decreases the mean lifetime of ligand-receptor complexes. Thus cells stimulated to divide by addition of a lectin would show a decreased response in the presence of an electric field.

Nuccitelli and Erickson (1983) and Erickson and Nuccitelli (1984) report that quail fibroblasts display "galvanotrophism" at field strengths of 1-10 mV/mm; field strengths greater than 400 mV will induce cells to elongate. Collectively their data suggest that weak E-fields could influence embryonic cell development. These results are particularly relevant in view of the reports by Delgado et al. 1982 and Ubeda et al. 1983 showing very weak, low frequency pulsed magnetic fields (10, 100, 1000 Hz and 0.12 and 1.2 μT) induced teratogenic effects in developing chick embryos. Further, these data suggest that pulse shape may be a critical parameter in the teratogenic effects observed.

Persinger and Coderre (1978) report that perinatal exposure of rats (2.5 days before and 2.5 days after birth) to a rotating 0.5-Hz magnetic field between 10^{-3} T to 10^{-6} T increased the number of thymic mast cells. The difference in mast cell number was still evident after 200 days; exposure of adult rats to the same field did not affect the number of thymic mast cells. In another experiment, rats were perinatally exposed to the same field intensities (described above) and examined for alterations in either thyroid function or morphology; no significant effects were observed (Lafreniere and Persinger 1978).

In a pulsed magnetic field study, Goodman, Bassett, and Henderson (1983) showed that exposing dipteran polytene chromosomes to a single pulse (380-μs, rep rate 72-Hz) magnetic field for 15 min, increased the specific activity of m-RNA. Alternatively, application of a pulse train (200-μs burst, rep rate 15 Hz) increased the specific activity of m-RNA after 45 min of exposure. These data again demonstrate the critical nature of the applied wave form in affecting cellular responses.

Continuous exposure (7 days) of <u>Pisum sativum</u> roots to 60-Hz E-fields (150 V/m to 430 V/m) resulted in a decreased growth rate at the higher field

8.5 G with an induced E-field between 1.9×10^{-2} V/m to 3.8×10^{-2} V/m) to PC-12 phaeochromocytoma cells and measured the release of ^{3}H-noradrenalin. Their data showed that field exposure elevates noradrenalin release about 27%; the effect was inhibited by adding exogenous Mg^{++}. The effect of Mg^{++} was ascribed to interference with Ca^{++} binding sites on the cell membrane.

Batkin and Tabrah (1977) exposed transplanted neuroblastomas to a sinusoidal 60-Hz, 12-G magnetic field for 12 days; exposure to ELF-EMF was initiated 3 days following transplantation. Their data showed that tumor growth was initially slowed and that more free red blood cells were in the tumor area, leading them to conclude that the magnetic field exposure was affecting the blood vessels by increasing their fragility. By the 19th post-transplantation day, however, the ELF-EMF exposed tumors reached normal size.

When frog retinas were continuously exposed to 20 mT magnetic fields at 20 Hz, the response of cells to magnetic fields occurred in less than 5 ms, whereas cells responding to light required about 85 ms (Lovsund, Nilsson, and Oberg 1981). Lovsund et al. (1980) suggest that these field intensities are involved in the generation of magnetophosphenes. Based on the data generated from both these studies and exposures to E-fields only (Granit 1950), Lovsund and colleagues conclude that a common structure is being stimulated in the retina. They further suggest that the magnetic field effects might occur through the induction of eddy currents. However, as noted above, Liboff and colleagues (1984) present arguments against the suggestion that eddy currents can explain magnetic field effects.

Recently, Lin-Liu and Adey (1984) reported on the effects of pulsed E-fields on the distribution of Concanavalin A (Con A) receptors. In these experiments, frog myoblasts were subjected to square DC electric pulses and compared to controls subjected to a constant DC field. Their data show that Con A receptors redistribute when subjected to monopolar, pulsed E-fields. Thus, the uniform, pre-field distribution of receptors became asymmetrical and polarized toward the cathodic pole after field exposure. The extent of the asymmetric distribution depended on the pulse width, duration of exposure, frequency, and intensity. Con A asymmetry could be induced in 5 min at a field pulse intensity of 1.5 V/cm whereas at 0.3 V/cm, 150 min were required before receptor asymmetry could be detected.

from the proliferative layer of embryonic chick epiphysis. The E-field effect could be completely blocked by inhibitors of Ca^{++} or Na^{+} transport. Based on these data, the authors suggest that the fields generate cation fluxes that stimulate DNA synthesis. Exposing skin fibroblasts from chick embryos and bone cells from rat embryos to similar field strengths also stimulated the uptake of ^{3}HTdR whereas rat spleen lymphocytes were unaffected by the fields. One problem in interpreting these results is that the intense E-field may be inducing a localized breakdown in the membrane. Stated in another way, is the observed bio-effect a result of the dielectric breakdown of the membrane or of a more subtle macromolecular rearrangement in the membrane?

Neonatal islet cells from pancreas, subcultured and exposed to low intensity DC magnetic fields (1 to 10 G), appeared to attach to the substrate and migrate to a greater extent than their respective non-exposed controls (Hayek et al. 1984). Of more interest, exposure to a homogeneous magnetic field stimulated insulin release at low concentrations of glucose and inhibited insulin release at high concentrations of glucose. Since one would normally expect diminished insulin release at low glucose concentration and elevated release at the higher concentration, it appears that magnetic fields can facilitate insulin release in the absence of the normal physiological stimulation. It is not clear, however, why the field inhibited insulin release in the presence of stimulating concentrations of glucose Jolley et al. (1983) reported that rabbit islets subjected to an 18-h pulsed magnetic field (4-kHz pulse bursts, repeated at 15-Hz intervals) showed altered Ca^{++} fluxes and diminished insulin release when the glucose concentration was elevated. Data in the literature indicate that elevated glucose levels in islet cells depolarizes and repolarizes the cells as a result of Ca^{++} movement into intracellular spaces (Hedeskov 1980). Both ELF-EMF research groups suggest that the fields are interacting with the membrane and may be modulating the movement of Ca^{++}.

Zurgil and Zisapel (1983) exposed fetal rat brain neurons to a pulsed field (10-Hz, 75-V, 0.8-ms pulse duration for 90 s) and noted a Ca^{++} dependent increase in the phosphorylation of a 43,000 d protein and a decrease in a 55,000 d protein. Unfortunately, there is no way that current density can be determined from the paper.

Dixey and Rein (1982) applied a pulsed magnetic field (500 Hz, 1.6 G to

subjected to amplitude modulated sinusoidal fields (6 to 100 Hz) using a radio frequency carrier. Bawin, Adey, and Sabbott (1978); Bawin, Gavalas-Medici, and Adey (1973); Bawin, Kaczmarek, and Adey (1975); and Blackman et al. (1978) reported that exposing embryonic chick brain to a 147- and 450-MHz carrier wave modulated at 9, 11, and 16 Hz resulted in a small but statistically significant increase in Ca^{++} efflux at 16 Hz. In contrast, exposing cerebral tissue from the cat and chick to 1-, 16-, 32-, and 75-Hz sinusoidal E-fields at 5, 10, 56, and 100 V/m suppressed Ca^{++} efflux at 6 and 16 Hz with thresholds around 10 V/m for chick and 56 V/m for cat cortex (Bawin and Adey 1976). Thus, a tissue exposed to a modulated RF wave showed enhanced Ca^{++} efflux whereas the opposite effect was found with ELF exposure. Blackman et al. (1982) attempted to replicate the sinusoidal studies reported by Bawin and her colleagues; they observed an enhancement of Ca^{++} efflux at 16 Hz, rather than a decrease, but reproduced Bawin's observation of no effect at 1 and 30 Hz. In essence, the experiment was replicated but with the two groups reporting opposite results. Nevertheless, on the basis of these data it has been proposed that both a frequency window and a power density window exist. In a related study, Lin-Liu and Adey (1982) exposed isolated synaptosomes to 450-MHz carrier wave modulated at 16 Hz and observed a 38% increase in the rate of Ca^{++} efflux; exposure to unmodulated carrier waves had no effect.

In a review of these experiments, Myers and Ross (1981) suggest that procedural and statistical non-conformities render the conclusion of the two groups unsettled and open to further experimentation.

CELL CULTURE EXPERIMENTS

The exposure of human fibroblasts to sinusoidal fields (15 Hz to 15 kHz) at magnetic field intensities of 2.3×10^{-6} T to 5.6×10^{-4} T resulted in enhanced DNA synthesis as assessed by the uptake of ^{3}HTdR (Liboff et al. 1984). A dose-response relationship was not reported even though the field intensity differed by several orders of magnitude. Liboff and his co-workers suggest that the magnetic field interaction is, therefore, independent of the time derivative (dB/dt) of the magnetic field. Enhanced incorporation of ^{3}HTdR into DNA was reported by Rodan, Bourret, and Norton (1978) using a high intensity oscillating 5-Hz E-Field at 1166 V/cm on chondrocytes isolated

Although the biological significance of these reports is difficult to assess, the fact that part of the immune system responds to amplitude modulated fields, albeit in a transient manner, dictates that additional data be obtained to clarify a potential problem.

CATION TRANSPORT

Batkin et al. (1978) exposed mice to a sinusoidal 60-Hz, 55- to 60-G magnetic field for 11 days. The mice were killed, and their kidney cortex and diaphragm tissue were isolated. A significant decrease in the Na^+ transport activities was observed in these tissues. In a related experiment they looked at liver and neuroblastoma Na^+ transport at 11 and 17 days. Their data indicate that both tissues showed depressed Na^+ transport at day 11; however, by day 17 the liver returned to control levels while the neuroblastoma remained in a depressed state. The kidney and diaphragm Na^+ transport was not determined following the longer field exposure. Teissie and Tsong (1981) reported that erythrocytes exposed to a 1-kHz AC fields at a field intensity of 10 V/cm induced membrane channels (including the Na-K-ATPase) to open. These field strengths will hyperpolarize the membrane by about 6 mV. The authors reported a 20% increase in the Na-K pump without a concomitant increase in the consumption of ATP. Further, the time a channel was open apparently decreased with increasing field strength reaching a plateau at 24 V/cm. In other words, at 10 V/cm the channels close with a half time of 10 s diminishing until a plateau of 2 s is reached at 24 V/cm. In addition, externally applied E-fields appeared to drive K^+ against its concentration gradient. Recently, Serpersu and Tsong (1983) applied a 1-kHz AC field at 16 V/cm to erythrocytes and examined the uptake of Rb^+. Their data show that an external AC field can stimulate the uptake of Rb^+; at low temperature (3° C) Rb^+ uptake was still observed whereas the Na-K pump was virtually inactive. Rb^+ uptake also displayed a frequency dependence peaking at 1 kHz and diminishing at 1 MHz. The effective range of uptake ranged between 100 Hz and 0.1 MHz. This observation is important because the uptake of Rb^+ cannot be simply explained by Joule heating. Thermal effects would not show a frequency dependence unless SAR'S show a frequency dependence due to characteristics of either the sample or the field application apparatus.

Several studies report effects on Ca^{++} efflux when tissues are

dedifferentiated. The addition of Ca^{++} transport inhibitors such as $LaCl_3$ inhibited dedifferentiation, whereas Ca^{++} ionophoreses stimulated the process. The investigators suggested that the dedifferentiating effect of the applied field is either occurring in the boundary layer of cell Ca^{++} or is mediated by the cell membrane. In any event, the net effect was to facilitate the influx of calcium. In a contrasting report, Chiabrera et al. (1979) induced erythrocytes to dedifferentiate by increasing the exogenous Ca^{++} concentration. When a pulsed field was applied, dedifferentiation was inhibited. However, if the pulse rate was changed, dedifferentiation could be enhanced. These apparently conflicting reports are typical of the bioeffects literature on ELF-EMF effects. They reinforce the apparent fact that subtle changes in parameters associated with the applied field (wave form, frequency, etc.) can produce markedly different bio-effects.

In related experiments, lymphocytes were exposed to RF carrier waves (147 to 450 MHz) that had been amplitude modulated between 6 and 100 Hz (Byus et al. 1984; Lyle et al. 1983; Sultan, Cain, and Tompkins 1983). Based on the data available to date, the unmodulated carrier wave does not appear to affect the cells. When a murine cytotoxic T-lymphocyte line was exposed to a 450 MHz, sinusoidally amplitude modulated at 60 Hz, their cytotoxic function was inhibited (Lyle et al. 1983). The cytotoxic effect was frequency dependent; it was reduced at both higher and lower frequencies. It was also reversible, disappearing 12.5 h after field exposure. Byus et al. (1984) examined the effect of amplitude modulated fields on C-AMP dependent and non-dependent protein kinases and found that the former were not affected by field exposure. In contrast, the non-C-AMP-dependent kinases showed a substantial (50%) loss of activity following 15- and 30-min exposures to 16-Hz fields and a smaller reduction (20%) with 60-Hz modulation. In both cases, activity returned to control levels with 60 min of exposure. Sultan, Cain, and Tompkins (1983) failed to detect any effect on the capping of B lymphocytes exposed to a 147-MHz RF carrier modulated at 9, 16, and 60 Hz.

In an attempt to evaluate the effects of in vivo exposure on the humoral response, mice were exposed to 60-Hz E-fields, at .15 to .25 kV/m for 20 h/day for 30 to 50 days. No significant differences were found in either the primary antibody response or in the mitogen stimulated response of spleen cells (Morris and Phillips 1982).

the post-exposure period before adding PDS diminished the effect of the drug on survival.

Tabrah et al. (1978) exposed heat synchronized Tetrahymena to 60-Hz, 60-G H-fields and noted a 3-h delay in the onset of division in addition to various cytomorphological changes. Similar results were also obtained with populations exposed for 49 h. Both synchronized and non-synchronized cells exhibited an increase in O_2 consumption when exposed to more intense magnetic fields of 100 G, at 60 Hz.

Continuous exposure of the slime mold, Physarum polycephalum, to ELF-EMF (45 to 75 Hz, 0.4 to 2.0 G, and 0.14 to 1.0 V/m) lengthened the mitotic cell cycle and depressed the rate of respiration (Goodman, Greenebaum, and Marron 1976, 1979). An altered cell cycle was also observed in cells exposed to 60-Hz, 1.0-G (H-only) ELF-EMF fields (Greenebaum, Goodman, and Marron 1982). Simultaneously applied E- and H-fields produced somewhat larger changes though the changes observed were not as large as the arithmetic sum of the effects of the individual fields. Intermittent exposure (16 h/day, 5 days/week) to 76-Hz, 1.0-G, 1.0-V/m ELF-EMFs also lengthened the mitotic cell cycle; however, the respiration rate increased rather than decreased, as observed with continuous exposure (Goodman et al. 1984). In a review of the mitosis experiments reported by Goodman, Greenebaum, and Marron (1976) the National Academy of Sciences (1977) criticized the data because mitosis was not scored in a blind manner. Subsequently, two other papers on mitosis have been published (H-fields only and intermittent E + H) in which blind scoring was applied and delayed mitosis was observed (Greenebaum, Goodman, and Marron 1982; Goodman et al. 1984). However, there have been no independent experiments to replicate this work. In a related set of experiments, Marron et al. (1983) reported that exposing Physarum amoebae to 60-Hz, 1.0-G, 1.0-V/m fields alters the cell's surface properties as determined by their partition coefficients in a two-phase aqueous polymer system. The two-phase polymer system has been used extensively to separate cells based on differences in their surface properties (Walter 1977).

LYMPHOCYTES, ERYTHROCYTES AND THE IMMUNE SYSTEM

Smith, Thomas, and Frasch (1979) exposed frog erythrocytes to pulsed DC fields of 50 mV/cm (10-ms on-off duty cycle) and observed that the cells

Hulsheger, Potel, and Niemann (1983) exposed a variety of microorganisms to high intensity bursts of pulsed E-fields (2 to 30 pulses/burst) at 20 kV/cm (pulse time delay 35 μs) and a repetition rate of 0.5 Hz. In general, they found that gram positive bacteria and yeast (S. aureus, L. monocytogenes, and Candida albicans) were less sensitive to E-fields than gram negative cells (K. pneumoniae, E. coli, and Pseudomonas aeruginosa). Cells in the log phase of growth were more susceptible to E-fields than stationary phase cells; exposure to 30 pulses at 20 kV/cm resulted in survival of 1%. Cells killed by the 30 pulse regimen leaked nucleotides and cofactors (AMP, ADP, NADH, etc.) but no intracellular enzymes were found. Examination of the field-perturbed cells indicated that the damage was most evident on the inner membranes.

The "mirror image" experiment was performed by Moore (1979) who exposed various microorganisms (C. albicans, Bacillus subtilis, Staphylococcus epidermidis, P. aeruginosa, and Halobacterium halobium) to 0- and 0.3-Hz square, triangular, and sine wave forms at field strength of 50 to 900 G. His data indicate that growth was generally stimulated at 150 G and inhibited at 300 G; the gram negative bacteria (P. aeruginosa and H. halobium) showed a somewhat greater stimulatory growth response to H-field exposure. Growth stimulation was correlated with the higher frequency (0.3 Hz) while static fields (DC) tended to be inhibitory. In these experiments changing the shape of the applied wave form shape (triangular, square, or sinusoidal) had no effect on growth.

The experiments performed on bacteria and yeast suggest that sensitivity to ELF-EMF may be a function of both the microorganism and its physiological state at the time the field is applied. If the "intensity windows" shown in some experiments prove to be real, it may explain why some investigators find ELF-EMF effects while others do not.

Protozoa and Slime Molds

Ripamonti, Ettienne, and Frankel (1981) exposed the ciliated protozoan, Spirostomum ambigium, to high intensity DC magnetic fields of 12.5 T (125,000 G). A 2-h exposure produced no discernible effects although the ability to survive in the presence of the drug 2,2'-dipyidyldisulfide (PDS, a sulfhydryl oxidizing agent) was diminished. This interaction was observed whether the drug was added during or following H-field exposure. Increasing

nutrient was added during the growth assessment period. Since all of the cultures were apparently kept in a non-growing state, it is not clear exactly how the investigators assessed growth.

In a related experiment, Aarholt, Flinn, and Smith (1981) exposed E. coli to square wave magnetic fields between 0.48 mT to about 20 mT at 16.66 Hz and 50 Hz. Fields of various intensities applied at 50 Hz had no effect until a reported threshold of 4.8 mT, whereupon the mean generation time (MGT) was reported to decrease. As the magnetic field intensity was further increased, MGT increased but continued to remain below control levels. Changing the applied frequency to 16.66 Hz (the 3rd sub-harmonic of 50 Hz) and incrementally increasing the field intensity resulted in a decrease in the MGT that began in the region of 0.5 mT and eventually plateaued at about 12 mT. The periodicity claimed by the investigators is difficult to discern; although, the data suggest that a frequency dependence or "window" may exist. We are somewhat confused by these data since ELF-EMF application stimulated the MGT of cells relative to the controls at a few intensities and frequencies, while at most of the field intensities the MGT is depressed. It appears that the real issue is the degree of inhibition induced by field exposure since, with a few exceptions, the MGT of ELF-EMF exposed cells remains below that of the controls. Thus, the suggested periodicity appears to be more a function of how much a given exposure regimen depresses growth relative to the controls rather than the absolute increase or decrease in the MGT.

In another experiment, Aarholt, Flinn, and Smith (1982) examined the effect of 50-Hz (square wave) magnetic field between 0 and 0.7 mT on the synthetic rate of the inducible enzyme B galactosidase. These data show that the synthesis of the enzyme relative to non-exposed controls was dependent on the applied field strength, in addition to showing the periodic responses discussed above. Of particular interest in this paper is the relationship between the effect of the H field and culture density. The field effect appeared to be at its maximum level at a density of 3.6×10^7 to 5.0×10^7 cells/ml (cells at this growth density are about 30 μm apart on the average); at a density above 10^8 cells/ml, when the cells average 20 μm apart, no effect was observed. In addition to an apparent cell density relationship, the authors suggest that the fields may be interacting at the genomic level of DNA/RNA/repressor protein.

the ambient ELF-EMF fields encountered by control cells. In the absence of such data, we have assumed that adequate shielding and/or appropriate precautions have been undertaken.

With few exceptions, most investigators of ELF-EMF effects have applied either a magnetic field alone (H only) or an electric field alone (E only). In attempting to assess the "potential hazard of ELF-EMF exposure" it is important to remember that both field components (E + H), as well as the earth's steady field, will be present. Further, depending on the source of the ELF-EMFs the intensity of the individual E and H fields will vary. In other words, in hazard assessment, caution is required when extrapolating potential environmental effects of electromagnetic fields based on data obtained from E-only experiments or H-only experiments.

As in most research into potential biological effects of electromagnetic fields, dosimetry is often a problem in the reports reviewed here. Many investigators have obviously made careful attempts to describe their exposure conditions, but either have provided rather sketchy descriptions or have omitted information that was not thought to be relevant at the time of the studies. For instance, reports of exposures to square waves and pulses often omit measurements of the rise times and decay times. These are related to the relative strength of the higher harmonics of the fundamental frequency. Work in the past few years with pulsed fields, such as those used therapeutically in promoting fracture healing, indicates that risetime figures may be important.

GROWTH EFFECTS OF WEAK FIELDS

Bacteria and Other Microorganisms

Ramon, Ayaz, and Streeter (1981) exposed the bacterium Escherichia coli to sinusoidal fields (60 and 600 Hz) at magnetic field intensities 3×10^{-3} T (30 G). They report that about 60 h of exposure to 60-Hz fields decreased growth 43%, a 54% decrease was observed when cells were exposed to 600 Hz. Electron micrographs of the exposed cells indicated the loss of flagella and a rupture of the cell wall. One problem in assessing this experiment is the fact that the cells were kept at 0° C during both the exposure period as well as during all subsequent manipulations. Further, the cells were starved and washed to remove all nutrients prior to exposure; no

A REVIEW OF CELL EFFECTS INDUCED BY EXPOSURE OF EXTREMELY LOW FREQUENCY ELECTROMAGNETIC FIELDS

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INTRODUCTION

The intent of this review is to assess the published data on the effects of extremely low frequency electromagnetic fields (ELF-EMF) on individual cells. In selecting papers for discussion, we restricted ourselves to reports that had been subjected to the peer review process; as a result, meeting abstracts and program reports have not been included. Our search centered primarily on ELF-EMF effects on single cell systems; although, where relevant, we digressed and included tissue effects. The selection of fields was restricted to frequencies less than 100 Hz except in those experiments where radio frequency (RF) waves were used as carriers of the lower frequency signals. All wave form shapes are included; where not otherwise noted, sinusoidal signals should be assumed. Electric (E) and magnetic (H) field intensities were not restricted unless they were totally irrelevant to the general purpose of this review.

To date, research on ELF-EMF cell interactions have primarily focused on questions of growth effects and/or related phenomenon such as cation transport. In attempting to explain how weak ELF-EMFs might alter the physiological state of the cell, many of these results have been used to extrapolate and implicate the cell membrane as a primary site of interaction. We intend to present and assess the data that suggest ELF-EMF exposure can affect the cell as well as those experiments that show no cell effects. We also intend to examine the hypothesis that the cell surface is a primary site of ELF-EMF cell interaction.

Experiments to ascertain whether weak fields can affect growth have been performed on numerous cell systems with a variety of field exposure regimens. One factor common to most of these experiments is the lack of information on

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THE EFFECTS OF ELF ELECTRIC AND
MAGNETIC FIELDS ON ARTIFICIAL CARDIAC PACEMAKERS

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INTRODUCTION

The artificial cardiac pacemaker presents a unique opportunity for interaction between and electric and magnetic fields and man. The basis for this is the fact that artificial cardiac pacemakers have 2 basic functions: (1) to provide periodic electrical stimulation to initiate a heart beat, and (2) to detect the occurrence of intrinsic heart beats so as to prevent competition between the heart and the artificial pacemaker for control of the heart rhythm. The purpose of this paper is to review the present knowledge concerning the potential for extremely low frequency (ELF) electric and magnetic fields to mimic intrinsic cardiac activity and thus affect pacemaker function.

ARTIFICIAL PACEMAKER APPLICATION AND DESIGN

Abnormalities of the cardiac rhythm may be divided into two major categories, those of impulse conduction (or heart block) and those of impulse initiation (asystole). Normally the heart is "paced" by the sinoatrial node, a group of cells located in the upper right atrium which are capable of spontaneous rhythmic depolarization. The firing rate of these cells is controlled largely by the autonomic nervous system, allowing significant variations in heart rate in response to the body's changing need for cardiac output. Impulses are conducted from the right atrium to the ventricles via the A-V node and His-Purkinje system. These structures form a specialized conducting system within the heart, and are the only pathway in the normal individual from the sinus node to the ventricles, the principle pumping chambers. Since the late 19th century it has been recognized that acute loss of consciousness and death may result from either a permanent or intermittent failure of these conducting structures (A-V block). In the first half of this

century a number of investigators explored the use of electrical pulses as a method of induction of ventricular depolarization during A-V block. The first method to be applied clinically was the passage of current between electrodes applied to the chest wall. Within a decade battery powered, fully implantable pacemakers were in clinical use, attached directly to the heart by an insulated wire placed through the venous system to the interior of the right ventricle. In the late 1960s and early 1970s disorders of impulse initiation were added to the list of clinical applications for artificial cardiac pacemakers. These disorders generally take the form of the Bradycardia-Tachycardia or Sick Sinus Syndrome. Like patients with intermittent A-V block, those with Sick Sinus Syndrome may suffer transient loss of consciousness or feelings of dizziness and light headiness. Though in general, patients with Bradycardia-Tachycardia Syndrome are less dependent on their pacemakers than patients with complete atrioventricular block. At the present time, slightly over half of all patients receiving implanted cardiac pacemakers do so for one of the various forms of the Bradycardia-Tachycardia Syndrome. Over the past two decades this has led to larger numbers of pacemakers implanted but a smaller fraction of pacemaker patients who are completely dependent on their pacemaker for the initiation of a heart beat. At present there are approximately 60,000 new pacemaker implants and 40,000 pacemakers replacements annually. The total pool of pacemaker patients in the United States is estimated to be approximately 350,000 to 500,000 individuals of whom perhaps one fourth may be considered pacemaker dependent.

An implantable pacemaker or pulse-generator consists of two basic functiona modules. The first is the output circuit, designed to draw current from a battery and deliver that current to the heart, via the electrode, in an appropriate amount, for an appropriate period of time, and at appropriate intervals. In newer devices, the timing functions of the output circuit are controlled by a microprocessor. The second module is for the sensing or detection of intrinsic cardiac activity. Sensing circuits were developed out of a desire to provide noncompetitive pacing. Such a pacemaker functions in the "demand" mode--that is, it only suppplies pulses if the heart fails to do so in a preset period of time. When the pacemaker is not stimulating the heart, it is constantly monitoring the electrode for evidence of electrical activity. A typical sensing system consists of (1) an amplifier to increase

the small biological voltages of cardiac depolarization to those that can be processed by electrical circuits, (2) filters to attenuate elements of the amplified signal that are likely to be unrelated to intrinsic cardiac activity, (3) a level detector to determine whether the filtered signal meets preselected amplitude criteria, and (4) a noise sensing circuit which attempts to eliminate environmental electromagnetic interference by means other than selective filtering.

Filtering is done in a band-pass fashion with the center frequency between approximately 20 to 50 Hz depending on the pacemaker model and manufacturer. This corresponds to the intrinsic frequency content of local myocardial depolarization as recorded on a standard pacing electrode. Thus since many ELF signals are within these frequencies, pacemaker filtering is relatively inefficient in eliminating them.

During the cardiac cyle the pacemaker also monitors the electrode for what it considers to be noise. In general, noise, as defined by pacemaker circuits, is characterized by repetitiveness. Intrinsic cardiac signals are periodic (1 to 3 Hz), lasting only for 30 to 100 ms and generally consisting of a single biphasic wave form. Most electromagnetic interference is composed of continuous, rather than periodic, wave forms and thus may be discriminated from intrinsic cardiac activity by this characteristic. The frequency of occurrence above which the pacemaker will classify a signal as noise is quite low, usually on the order of 4 to 15 Hz, well below the power frequency spectrum. If noise is detected, the pacemaker responds by disabling the sensing system and thereby reverting to an asynchronous mode. The pacemaker will continue to pace asynchronously until noise is no longer detected. In this way the pacemaker is able to avoid false inhibition; though competition with normal heart beats may result if an intrinsic cardiac rhythm is present. This asynchronous mode is also frequently termed the reversion or noise mode. Therefore the cardiac pacemaker depends primarily on its noise reversion system rather than band-pass filtering for protection against false inhibition by most ELF signals.

There are two basic designs of cardiac pacing systems. These are usually referred to as bipolar and unipolar though both obviously employ two poles. The clinical term, bipolar, refers to a pacemaker with two wires which attach to the heart (both the anode and cathode) so that current is passed for only a

short distance through the cardiac tissue from one pole to the other. A unipolar pacing system, on the other hand, has only a single wire attached to the heart, the cathode. The case of the pulse-generator serves as the anode. Current is passed from the electrode in the heart through the myocardium and tissues of the chest to the pulse-generator case which may be located either in the upper chest just beneath the left or right clavicle or in the left upper quadrant of the abdomen. The infraclavicular location is presently used in over 90% of patients.

The unipolar pacemaker differs significantly from the bipolar with respect to the potential for electromagnetic interference. With a unipolar pacemaker there are large differences in electrode size and a large dipole which, in most cases, has both horizontal and vertical components. This geometry provides a large "antenna loop" effect for coupling to magnetic fields and for little common mode rejection of electrical fields. Bipolar systems, in contrast, have very small dipoles, usually less then 3 cm, and only minor differences in electrode size. In addition, the dipole is typically oriented in the horizontal plane, with little vertical component.

THE CLINICAL SIGNIFICANCE OF ELECTROMAGNETIC INTERFERENCE

Over the past two decades a variety of exogenous and endogenous sources of electromagnetic interference have been identified. The hazards presented by many of these environmental sources--including microwave ovens, automobile engines, field and leakage currents from electrical appliances, electrical transmission facilities, anti-theft devices, escalators, airport weapon-detectors, radar, radio transmitters, X-ray machines, diathermy, electroshock therapy, and a variety of other hospital and dental equipment--have recently been reviewed (Sowton 1982). Despite the enormous list of potential sources of interference (only a few representative ones are listed above), reports of clinical events resulting from exogenous electromagnetic interference are rare. Sowton (1982) suggests, "that it is impractical to advise patients to avoid all of them (sources of interference) even if it were possible to identify them in advance. The patients should be told in general terms about the possibility of interference but assured the risks are extraordinarily low." The most common source of clinically significant interference is the endogenous generation of skeletal muscle

myopotentials in proximity to the pulse-generator case of a unipolar pacing system. These are reported to be clinically significant in 14% of patients and to occur in nearly half of all patients who are carefully tested (Secemsky et al. 1982).

SUMMARY OF STUDIES OF POWER FREQUENCY INTERFERENCE

Bridges and Frazier (1979) conducted a comprehensive series of in vivo and in vitro experiments designed to determine the response of implanted cardiac pacemakers to 60-Hz interference and the nature of that response. The investigators tested 13 devices by applying a 60-Hz voltage level directly to the terminals. Using this test system, the voltage necessary to effect the pacemaker ranged from 0.45 to 1.2 mV but generally was in the range of 0.5 to 1.2 mV. They also characterized the nature of the effect which was, in most cases, reversion to asynchronous pacing. However, in two of the first eight devices tested a small "window" of input voltages produced aberrant pulse-generator responses. Findings were similar when the investigators tested three additional units by the same manufacturer. Though the magnitude of the window was quite small for most pacemakers, it was 0.75 mV in one.

The investigators also set out to determine, both by noninvasive and invasive studies (in human subjects and primates respectively), the transfer factors between a vertical electric field, induced body currents, and the potential differences that these currents could produce across the poles of both bipolar and unipolar pacemakers implanted in man. Using data derived largely from primates with pacemakers implanted, the investigators made predictions about the magnitude of a vertical field necessary to induce reversion in a pacemaker implanted in an average sized man standing upright in the field. The estimates for a spectrum of pacemaker sensitivities and lead configurations are shown in Table I.

The authors further demonstrated that body position had significant effects on the developed voltage. For example, if the arms were raised above the head, the electrical field required to produce a given interference voltage fell by 40 to 50%. Thus, body movement within a vertical electrical field continuously modulates the voltage developed at the pacemaker input.

The issue of windows of aberrant behavior was further raised in a report of Jenkins and Woody (1978). They found that 38 of 57 units tested in their

laboratory demonstrated some aberrant behavior when exposed to ELF interference. The mean input voltage for reversion to the asynchronous mode was 1.25 mV, the level for aberrant behavior was 0.56 mV. Devices were also subjected to magnetic fields. Thirteen of 26 units reverted at a mean field intensity of 1.5 G while seven exhibited aberrant behavior. The remaining six units were unaffected by fields up to 20 G.

TABLE I

CALCULATED ELECTRIC FIELDS
NECESSARY FOR REVERSION*
(in kV/m)

PACEMAKER SENSITIVITY	LEAD CONFIGURATION		
		UNIPOLAR	
		Vertical Separation	
	BIPOLAR	8 cm	12 cm
LOW	600	171.0	91.0
MEDIUM	50	14.3	7.6
HIGH	23	6.4	3.4

*From Bridges and Frazier (1979)

These two studies strongly suggested that exposure to vertical ELF electric fields or other contact with ELF signals such as leakage currents from household or occupational electrical devices could result in body currents sufficient to produce pacemaker reversion. In addition, some pacemakers might exhibit windows of aberrant activity at subreversion levels. Because no information was given in either study with respect to the dates of design or production of the devices tested, their manufacturers, or the distribution of units among models or manufacturers, it was not possible to assess the impact of the findings on the pacemaker implant population. Certainly one must remember that all of the units in both were probably manufactured prior to 1977 since results from both studies were available in 1978.

The predictions of Bridges and Frazier (1979) and Woody and Jenkins (1978) were tested by exposing patients with implanted pacemaker systems to high intensity, vertical, 50-Hz electric fields. In a preliminary study in Great Britain, Butrous et al. (1982) tested 10 patients with a single model of unipolar pulse-generator. None of these patients exhibited aberrant function, in fact, despite the use of unperturbed 50-Hz fields of up to 20 kV/m and induced body currents of up to 300 μA, these devices did not even revert to the asynchronous or noise mode.

More recently, these same investigators published results from 35 patients having 16 different pacemaker models from six manufacturers (Butrous et al. 1983b). Again, applied fields up to 20 kV/m were applied, inducing total body currents from 10 to 337 μA. The body currents necessary for reversion to the asynchronous or noise mode differed among the various models and within a group of patients having the same model. The latter may have resulted from differences in body size and the vertical separation of the unipolar electrodes. Overall the field strength necessary for any effect was 5 kV/m or greater in all but two patients. The reversion currents varied from 26 to 200 μA. Reversion current also varied with the programmed sensitivity of the pacemaker.

Butrous et al. (1983b) confirmed the earlier findings of Bridges and Frazier (1979) that certain orientations of the body could alter the effect on the pacemaker even though the total body current remained constant. If the ipsilateral arm (in an infraclavicular implant) was raised, reversion occurred at lower total body currents than if the contralateral arm was raised.

Most importantly, the investigators replicated previous findings of aberrant pacemaker activity (Table II) (Butrous et al. 1983b). In two patients, pacemaker behavior exactly duplicated a "window effect" with a period of aberrant behavior which changed to reversion mode as the field strengths were increased. The observed windows were from 55 to 113 μA in one patient and from 104 to 121 μA in a second patient. In five additional patients the devises exhibited inhibition or irregular and abnormally slow pacing during electric field exposures above a given level. This type of aberrant behavior was found to occur at field strengths of 5 to 20 kV/m with induced body currents of 58 to 213 μA.

TABLE II

EFFECTS OBSERVED DURING PATIENT EXPOSURE +

MANUFACTURER	PACEMAKER RESPONSE NONE	REVERSION ONLY	WINDOW*	ABNORMAL*
MEDTRONIC	10			
TELETRONICS		11	1	
CORDIS				4
CPI		1		1
VITATRON	1	2		
PACESETTER		3	1	

+ From Butrous et al. (1983b)
* See text for explanation.

A similar study has been performed in the United States by Moss and Carstensen. Although this study has not yet been published, preliminary reports suggest that the findings are similar to those of Butrous et al. (1983b) (E. L. Carstensen, pers. com. 1984).

Butrous and colleagues also reported what they felt to be pacemaker interference in two substation workers (Butrous et al. 1983a). The first was a 32-year old man, implanted with a Teletronics pacemaker, who developed palpitations (i.e., irregular heart beats) upon returning to his occupation as an electrical engineer in a 275 kV substation. ECG monitoring during exposure to a vertical electric test field revealed reversion to the asynchronous mode with competitive pacing. A second substation worker, who had received a Cordis pacemaker, was tested before returning to work and found to have aberrant pacemaker activity at field strengths above 13 kV/m. Both individuals were outfitted with a protective garment which effectively shielded them from the electric fields and allowed them to resume their occupations.

SUMMARY

From the above data, we must conclude that the potential exists for interaction between ELF electric fields and implanted pacemakers. Initial in vitro and in vivo laboratory findings have been confirmed by actual patient exposure. ELF interference may have no effect on certain pacemakers, while others may undergo reversion to the asynchronous or noise mode and still others may exhibit aberrant activity. The levels of exposure necessary to effect a susceptible pacemaker system are quite variable (i.e., induced body currents of 26 to >200 mA). The response appears to vary largely according to manufacturer; with some manufacturers dealing with ELF interference much more effectively than other.

CONCLUSIONS

We must place pacemaker interference problems in general, and ELF electric and magnetic field interference in particular, in perspective. Clinically documented interference problems are extremely rare with the exception of the body's own endogenous myoelectric interference. First the potential for interference from ELF electric and magnetic fields must be compared to that resulting from exposure to sources of higher frequency interference such as microwave ovens; television sets; radio and television transmitters; and a host of business, medical, and occupational devices.

Even if the pacemaker is affected, the patient still may not be placed at risk. Reversion to the asynchronous mode is a design feature of modern pacemakers and presents little risk when it occurs for brief periods. In fact, patients are routinely placed in the asynchronous modes for evaluation of the pacemaker. This is done as often as monthly during telephone transmission of the ECG with the patient unattended in the home. Brief periods of competitive pacing are likely to be hazardous only in those situations in which the ventricular fibrillation threshold is markedly decreased, such as during a heart attack or severe electrolyte imbalance. Obviously, however, the potential for aberrant behavior of the pacemaker with cessation of pacing or markedly slowed pacing does present a hazard for that minority of patients who are dependent on the pacemaker for a cardiac rhythm.

Finally, our ability to more precisely quantify the risks posed by ELF electric and magnetic fields is limited by the lack of data. Presently there

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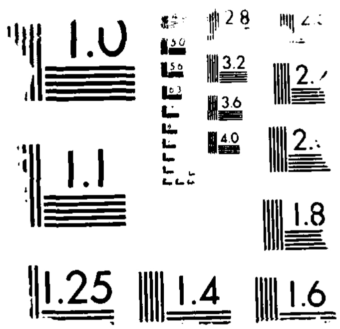

1.0
1.1
1.25
1.4
1.6
1.8
2.8
3.2
3.6
4.0

are probably over 200 pacemaker models in use of which fewer than 50 have been tested. Thus at present, only very rough estimates can be made regarding the numbers of susceptible individuals. For example, of the estimated 350,000 to 500,000 pacemaker patients in the United States, approximately half (i.e., 175,000 to 250,000) have unipolar pacemakers. Only 20% of this group would have devices produced by manufacturers whose devises have to date exhibited aberrant responses (i.e., 35,000 to 50,000). And of this group approximately only 25% are probably pacemaker dependent. Thus roughly 5,000 to 15,000 individuals may be at some risk from interference. At present little is known regarding exposure of these individuals to common sources of ELF or other forms of interference. Only when a more precise measure of the size of the susceptible population and their exposure is known can we fully assess the risks involved.

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BEHAVIORAL TOXICOLOGY OF ELF ELECTRIC AND MAGNETIC FIELDS

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INTRODUCTION

This review summarizes and evaluates the scientific literature (from 1977 to 1984) on the behavioral effects of exposure to electric and magnetic fields ranging in frequency from 1 to 300 Hz (ELF). Most of this work has been carried out at 60 Hz.

Much of what is known about the behavioral effects of exposure to ELF fields is summarized by a National Academy of Sciences report (NAS 1977). Since the time of that report, considerable research has been carried out to assess specifically the "health effects" of exposure to ELF fields. The impetus for this work comes from the United States Department of Energy and the public power industry, both here and abroad, because of their interest in identifying possible deleterious effects that might result from exposure to power-frequency (50- and 60-Hz) electric and magnetic fields. Because of their goals, much of the research emanating from these and other programs has been toxicological in nature--at least more so than in past researches. In other words, because of the implicit risk-benefit analysis that will eventuate from these studies, the researches are often cast in toxicologic context. Among other things this means most (but not all) of the work is well conceived and designed, correctly analyzed, establishes dose-dependence when an effect is obtained, attempts to replicate initial effects, attempts to generalize the existence of significant effects to more than one species, and attempts to evaluate established effects with regard to their being placed under the rubrics of "effect" or "hazard". Thus, a number of the behavioral effects of exposure to ELF fields, that have been identified since 1977, can be considered well-established effects. These constitute the majority of material reviewed in this paper. However, lessor effects are considered, and,

where relevant, their implication for our understanding of the behavioral toxicology of exposure to ELF fields are considered.

The principle behavioral effects reviewed in the following pages appear under the following ordered headings:

- Perception and Behavioral Detection
- Arousal Response and Activity
- Aversive Behaviors
- Neurobehavioral Teratology
- Behavioral Effects in Humans

Following this primarily behavioral review is a discussion of research needs with special reference to other well-established effects of exposure on neural systems. These include:

- Neuropathology in cerebellar Purkinje cells
- Efflux of calcium ions from brain tissue

BEHAVIORAL EFFECTS

Perception and Behavioral Detection

A number of vertebrate species are able to detect the presence of ELF electric and magnetic fields and they do so by a variety of means.

By far and away the most sensitive of these detection abilities is that termed "electroreception." Because this is such a large literature I will not review it in any detail here. The major developments in this area since the report by the National Academy of Sciences (NAS 1977) has dealt with identifying and differentiating the various forms of electroreception that appear in a number of fish. Bullock (1982) suggests that evolution "invented" electroreception at least three different times.

For our purposes it will suffice to indicate that there are two broad classes of receptors that respond, at least in part, to ELF electric fields. The low frequency receptors, known as Ampullary organs, have a frequency response of from 0.1 to 50 Hz. The high frequency receptors respond from 50 to 2,000 Hz, and are classed as Tuberous organs. The absolute threshold for behavioral detection in different species can range from as high as 10 mV/cm to as low as about 5 nV/cm. The latter sensitivity is for the Ampullae of Lorenzimi of the Elasmobranchs such as sharks, rays, and skates (Bullock 1982; Kalmijn 1985).

How such weak electric fields are transduced into classical neural firing patterns is not yet known. It seems unlikely that the local currents directly depolarize receptors because the fields to which these fish respond are several orders of magnitude below the voltage required for classical neuronal firing. Patch-clamp techniques should help unravel the biophysics of transduction in the near future.

Other species are also able to detect electric fields, although this occurs at much higher field strengths. Cooper et al. (1981) trained pigeons to respond on a variable interval 90-s reinforcement schedule. Once stable behavioral baselines were obtained, the pigeons underwent classical conditioning trials which used 60-Hz electric fields (25 or 50 kV/m; 10.5 or 21 kV/m at the pigeon's head) to cue an impending shock. Following sufficient training trials, the pigeons could then be probed with the electric field. Had they been able to detect the electric field during conditioning, then, when probed later, the pigeons would show conditioned suppression, i.e., they would suppress responding for food relative to their baseline behavior on the interval schedule. Cooper's pigeons suppressed at the higher field strength, but not at the lessor one. A second report from this lab (Graves 1981) assessed the pigeons with and without shielding by a Faraday cage. If the pigeons had suppressed responding because of cuing by stimuli other than the fields (e.g., noise, vibration) then they should suppress inside or outside of the Faraday cage. The results made it clear that the pigeons suppression was under electric field control. This is a well-done study that recognizes and tests for possible sources of artifact.

Stern et al. (1983) have similarly evaluated behavioral detection of 60-Hz electric fields in male rats. Their rats were trained to make a nose-poke operant on a parallel plate exposure system. Using a rigorous signal detection paradigm they found that the range of values bracketing the absolute threshold for detection of the electric field was between 3 to 8 kV/m. In a second study (Stern and Laties n.d.) female rats were similarly evaluated in a signal detection paradigm. Their thresholds were no different than that of male rats. Sagan (pers. com. 1982) has obtained virtually identical thresholds in male rats. Sagan also used a signal detection approach, although there are significant procedural differences in the two studies. Both of these detection studies using rats are well done; and the Stern et al.

study was very thorough in evaluating the possibility that their rats might be responding to some cue other than the electric field. Their data made it clear that they were not.

What these studies do not tell us is how these animals detect the electric fields to which they were exposed. Certainly, they do not have electroreceptors. What, then, is the "site of action?" The answer is "we do not know", although there are at least three possible sites of action. One is that the animals are affected by and may perceive the external fields; this would include such secondary effects as piloerection induced by the oscillating field forces. A second possibility is that the internal fields (i.e., fields in tissues) are somehow detectable. A third, and related, possibility is that the current flow produced by the internal fields is somehow detectable.

If we allow the human detection of electric fields to serve as a guide Reilly (1978), pigeons and rats probably detect the fields because of their effects on the surface of the body, e.g., piloerection. There are a number of studies in progress attempting to address the site of action question. However, for now, we can only guess that it is the external field forces that are perceived and responded to. Internal fields, and the related current flow that occurs, could possibly induce phosphenes. The currents demanded for this to happen would have to be larger than those induced by the low fields employed in these detection studies. For example, in man, the minimal current flow for phosphene induction is about 150 μA, if it is applied near the eyes; applied elsewhere on the head, it would take well over 200 μA to induce phosphenes (Adrian 1977).

Arousal Response and Activity

Another index of field perception/detection is the arousal response an animal shows to a stimulus. It is not as precise, nor is it as quantifiable, an index of perception/detection as those indices obtained from detection studies. But it does suggest some form of perception (i.e., an orienting response), given one rules out direct neural stimulation by ELF fields (e.g., of the reticular formation).

Hackman and Graves (1981) exposed an outbred strain of mice to 25 or 50 kV/m 60-Hz electric fields and determined plasma corticosterone levels at

various time intervals after exposure. In the first experiment these intervals were on the order of minutes; the second experiment on the order of hours; the third experiment was on the order of days. Positive controls were included which measured plasma corticosterone responses to social and auditory stressors. While the positive controls showed significant increases in plasma steroid levels (stress), the two groups exposed to electric fields were not different from one another nor from the sham-exposed/unhanded controls. The field-exposed groups did show a transient rise at 5 min after field onset, but were nearly normal by 15 min after field onset. The authors, appropriately, interpreted these transient changes as an orienting (arousal) response and not as indicative of stress.

A similar transient response was reported by Rosenberg, Duffy, and Sacher (1981). They exposed mice (Peromyscus leucopus) to 100 kV/m, 60-Hz electric fields. The animals were exposed for 1 h four times with 1-h intervals between each exposure. Gross motor activity, and a number of metabolic indexes were monitored throughout the 1-h exposures. These investigators found an immediate, but transient, increase in activity and an increase in the use/production of O_2/CO_2. These responses were not elevated following the second 1-h exposure. In a subsequent study, Rosenberg et al. (1983) were able to show that the threshold for the arousal response in their mice ranged between 35 and 50 kV/m. These values are reasonably consistent with the values Hackman and Graves found to effect their index of arousal. Similarly, the transient nature of the response is common to both researches.

Other investigators have reported ELF field-induced changes in activity and where there have been transient elevations, one is inclined to interpret them as reflections of arousal given the preceding findings. Hjeresen et al. (1980) exposed rats to an intense 60-Hz electric field in a study of "perception" and avoidance. At field strengths greater than 75 kV/m, rats tested in a lucite alley took residence on the side covered with a Faraday cage. However, rats tested at all field strengths (25 to 100 kV/m) showed increased activity in the first hour of the 23.5-h test, but not thereafter, when compared with sham-exposed controls.

In all of the foregoing studies, animals rapidly adapted to the novel electric fields to which they were exposed. Such was not the finding when Smith and Justesen (1977) exposed two strains of mice to a 60-Hz field with a

dominant magnetic component at 1.7 mT. The exposures were recurrent 120-s presentations of the field. Both strains (DBA/J and CD-1) showed significant increments in activity over all test sessions (i.e., they did not habituate from day to day over the 48 h of exposure). Of the two strains, the DBA's showed greater reactivity to the magnetic field's presence.

A number of studies which have exposed animals for longer durations have reported mixed findings--but these differences are probably related to procedure. For example, some investigators have found changes in adult activity as a result of prenatal exposure to ELF fields. Such studies are discussed in the section on Neurobehavioral Teratology. Other studies have exposed adult animals to ELF fields for longer durations and found minimal effects of exposure. Lovely, Creim, and Phillips (1984b) exposed rats for 30 to 37 days and, in two different studies (one at 1.9 kV/m and another at 40 kV/m), found no remarkable effects of exposure on post-exposure exploration, activity or its circadian distribution. The first study at 1.9 kV/m tested rats for only 1 h following a month of exposure to a 60-Hz electric field. Half the rats were tested in the morning and half were tested in the afternoon in a residential maze. Compared to sham-exposed controls there appeared to be a reversal of the early morning to late afternoon differences typically seen in this task. In the second study, at 40 kV/m, rats were tested in the same maze for 23-h periods following 30 to 37 days of exposure. The data showed no significant perturbation of the normal circadian distribution of activity as had been suggested by the findings at the lower field strength. One is inclined to dismiss the initial finding as a false positive, unless there is an intensity "window" at 1.9 kV/m.

Aversive Behaviors

Exposure of rodents to 50- or 60-Hz, primarily electric, fields will lead to aversive behavior if the fields are strong enough.

Bayer, Brinkmann, and Wittke (1977) observed that female rats, given the choice of two living environments connected by a runway, would traverse the runway to avoid exposure to a 50-Hz, 100 kV/m electric field. However, the female rats would re-enter the field during the nocturnal portion of the day-night cycle on which they were maintained. While this observation was obtained on only a handful of animals, the effect was later observed by

Hjeresen et al. (1980) for 60-Hz electric fields at, or above, field strengths of 75 kV/m. Hjeresen et al. also observed the nocturnal reversal seen by Bayer et al. Hjeresen et al. employed reasonable sample sizes of male Sprague-Dawley rats and found that the aversive behavior (1) develops within 45 to 60 min, (2) is unaffected by up to 1 month of prior exposure at intense (100 kV/m) electric fields, and (3) was able to eliminate electric shock, corona discharge, ozone, audible noise or vibration of the exposure system as sources of "artifact". The statistical analyses were appropriate for the data collected, and in a subsequent study Hjeresen et al. (1982) demonstrated similar phenomenon in Hanford Miniature Swine that had already been on exposure (20 h/day for up to 3,600 h) to a 30 kV/m 60-Hz electric field. Although the statistical analyses of the data in the latter study may not be the appropriate tests of significance, the data presented suggest that the effect is real. The data also makes it clear that the diurnal swine show the opposite effect of the nocturnal rat with regard to day-night dependence of field aversions. Thus, the pigs tend to remain in the field during the daylight hours and avoid field exposure at night.

Despite the fact that this aversive behavior appears to be robust and generalizes across species and test parameters, it would be premature to conclude that intense electric fields are an adverse stimulus that easily motivate aversive behavior in the species tested. Creim, Lovely, and Phillips (1982) employed the same test apparatus used by Hjeresen et al. (1980) and found that rats which experience electric field exposure in a slowly ascending sequence of field strengths (0, 25, 50, 75, and 100 kV/m, with each 1-h test carried out every 15 days) fail to avoid electric fields at field strengths up to 100 kV/m in the later tests. The study appears to be free from artifact, is well-designed (other groups with random or descending sequences of field strengths do show the typical field aversion), and is properly analyzed statistically. Thus, the nature of an animal's prior experience with the electric field may serve to completely attenuate the typically observed aversion.

Another study by Creim et al. (1984b) paired saccharin-flavored water with a 3-h exposure to 60-Hz electric fields at intensities up to 130 kV/m in an attempt to obtain taste aversion (TA) learning. When novel tastes, such as saccharin-flavored water, are paired with stimuli producing illness or malaise

generally (Garcia and Koelling 1967) or gastrointestinal distress specifically (Pelchat et al. 1983), the adversive agent is a sufficient condition for TA learning to occur in rats (and most other species). In a series of three experiments, Creim et al. failed to find evidence for TA learning as a result of electric field exposure up to 5 h in duration. They also failed to find any synergistic (additive) effect of combining cyclophosphamide (an agent which does produce GI distress) and electric field exposure for 5 h after consumption of saccharin-flavored water. They did find TA learning with cyclophosphamide alone, thus validating their procedures and experimental design. So, here is more evidence that allows one to narrow the possible interpretations of "aversive" behavior induced by exposure to electric fields.

Although rats may fail to show TA learning, they will avoid saccharin-flavored food when its consumption necessitates traversing an alley from the Faraday-shielded half of the alley to the half exposed to a 100 kV/m 60-Hz electric field (Creim et al. 1983). The effect is large, easily replicated (in the same laboratory), and is strictly contingent on the presence of the electric field. Indeed, the preference <u>for</u> saccharin is developed prior to any electric field exposure. Nevertheless, the preference is abandoned when consumption requires exposure (i.e., entry) to the electric field. This series of studies is well-designed and based on large sample sizes (original effect based on 18 rats/group). A rather tortuous series of subsequent experiments (Creim et al. 1984a) finally revealed that this apparently robust effect depended on as subtle a variable as whether the container holding the saccharin-flavored food was above, or below, the ground plane on which the animal was exposed to the 60-Hz electric fields. Finally, the most recent study by Creim (pers. com. 1984) has revealed that the saccharin-flavored food aversion is largely eliminated if the rats' vibrissae and eyebrows are shaved prior to testing. Of greater interest was the finding that the field aversion typically seen in the Pacific Northwest Laboratory studies (Hjeresen et al. 1980) was also greatly attenuated when the rats vibrissae and eyebrows were shaved prior to testing. One is inclined to conclude that the behavioral aversions are based on no more than stimulation of facial hair in the rat. If this interpretation is correct, then the extensive series of studies documenting behavioral aversions that result from exposure to 60-Hz electric fields may be unique to the rat, and possibly other species, that find stimulation of their facial hair a "adversive" experience.

Neurobehavioral Teratology

Neurobehavioral teratology refers to the early ontogenetic and adult neural and behavioral changes that occur due to perinatal exposure to a putative toxic agent or substance. It is one of the most sensitive "preparations" that can be employed by the behavioral toxicologist because subtle events happening in utero leave not-so-subtle markers on adult nervous system function, including behavior. The primary reason for this, if exposures are appropriately timed, is that differentiation and migration of neural cell types are not complete until well after birth. Perturbation of these processes will often manifest themselves as changes in the development of neural responses or in their adult expression or in both. More often than not, the adult changes are permanent.

It is another issue as to whether one decides to interpret adult behavioral change due to perinatal influences as an "effect" or a "hazard". In other words, one can not assume that all perinatal manipulations that produce neural changes are necessarily bad. Greenough (Turner and Greenough 1983) is one of a number of researchers that manipulate the quality and quantity of environmental stimulation that a rodent receives during rearing. Over the years profound effects have been shown to occur at all levels of neural organization--morphological, chemical, and behavioral.

When we turn to studies evaluating the neurobehavioral effects of perinatal exposure to ELF fields the safest generalization we can make is that there is an insufficient data base at this time to come to any sound conclusions regarding the putative toxicity of ELF fields.

Frey (1982) exposed pregnant Sprague-Dawley rats to a 60-Hz electric field at 3.5 kV/m from the first to nineteenth day of gestation. The experimental design allowed for cross-fostering within a day after parturition to eliminate postnatal mothering effects. The author claims a number of postnatal alternations in behavior, including open-field activity, but the detailed methods and statistics are reported in such minimal detail, it is difficult to evaluate this report.

Lovely, Creim, and Philips (1984c) also exposed Sprague-Dawley rats to a 60-Hz electric field at 60 kV/m. Exposures were for 20 h/day from conception to 21 days of postnatal age. There were no attempts to eliminate mothering effects, as this was a preliminary study. At ninety days of age male/female

one-day-old chicks to 1.3 G at 45 Hz for 28 days depressed their growth rate by 9 to 11% as compared with that of the unexposed birds; they observed a similar effect in an electric field of 3,500 V/m. In another study (92), they found that exposure of egg-laying hens to 1,600 V/m at 60 Hz for 16 weeks caused a decrease in egg production. Magnetic fields can also induce marked embryological changes (46).

We continuously exposed three generations of mice to a 60-Hz electric field and found that in the first and second generation, males and females reared in both fields were significantly smaller than the comparable control group when compared at 35 days after birth. In the third generation the males exposed to the vertical field were significantly smaller than the controls. In addition, the exposed mice exhibited a higher rate of mortality (114). In a follow-up study at 3,500 V/m (113), using an improved exposure system, we again found that the field caused an increased mortality in each generation; it also caused altered body weights in the third generation.

McElhaney and Stalnaker (104), of West Virginia University, applied 7,000 V/m, at 3 and 30 Hz, to the immobilized but intact femurs of rats. They found that the electric field lessened the process of bone resorption that usually occurs in an unused limb; additionally, many of the exposed rats, but none of the controls, developed bone tumors. These results were partially confirmed by Martin and Gutman, of West Virginia University (117); they found that the bone loss which accompanies disuse was lowered by the electric field.

Grissett et al. (65), at the Naval Aerospace Medical Research Laboratory, exposed 30 monkeys to 20 V/m and 2 G at 76 Hz. After one year, the field-exposed males were significantly heavier than the control males.

We studied the effect of 60-Hz electric fields of 1,000 to 5,000 V/m on the rate of fracture healing in rats (111), and found retarded fracture healing in the exposed animals at 14 days postoperatively.

EMF exposure has a general debilating effect on reproduction (3, 4, 76, 133, 170, 173).

Central Nervous System

Extremely low frequency (ELF) fields have been examined from the viewpoint of their effect on the brain by direct means and, in other studies, by means of the behavior modification that results from the exposure.

(45, 72, 79, 91, 126, 127, 132, 136, 149, 162, 164, 189, 190). Weak electrical signals have been used successfully for the treatment of drug addiction (137a), cancer (66, 128), pain (12, 13, 38, 47, 68, 88, 147), and for stimulation of normal healing (22). A broad range of organisms from bacteria to vertebrates have been shown to detect, exhibit, and respond to weak electric and magnetic fields (2, 5, 11, 25, 33, 48, 53, 61, 63, 80, 87, 94, 99, 102, 115, 116, 119, 125, 144, 148, 153, 156, 157, 167, 178, 179, 182, 183, 187, 188, 196).

Reports concerning the biological effects of weak electromagnetic signals can now be found in the literature of virtually all surgical specialties, physical medicine, dentistry, neurology, anatomy, biochemistry, clinical ecology, and many other disciplines and specialties. A new science is being born, and it is bright with the promise of benefitting humanity. One of the brightest promises involves the deeper understanding of the origin of disease. It is becoming increasingly clear that much illness is environmentally induced (150, 151, 152). This awareness brings into sharp focus the question of the chemical and nonchemical composition of our environment. If electromagnetic energy can produce a therapeutic result in the hands of a clinician, if detection of electromagnetic fields is part of the primordial apparatus of living systems, if ultraweak electrical signals can initiate and regulate the body's growth systems, then it is reasonable to expect that uncontrolled application of electromagnetic energy to living organisms would have adverse effects. Does electromagnetic pollution belong on the list of established and accepted environmental contaminants capable of causing disease? The direct evidence that requires an affirmative answer is outlined in the next Section.

HEALTH RISK OF EXPOSURE TO SANGUINE/SEAFARER FIELDS

Introduction

Numerous laboratory studies have described biological effects following exposure to nonthermal electromagnetic fields (EMF). Some of the studies and an analysis of their significance are given below. A more complete description is given elsewhere (16).

Growth and Development

Giarola and Krueger (59), of Texas A&M University, found that exposure of

ELECTROMAGNETIC FIELDS AND PUBLIC HEALTH

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INTRODUCTION

The roots of bioelectricity can be traced back past Galvani and Volta into antiquity, but bioelectricity was dormant, barely kept alive by the work of a few such as Lund (101), Burr (34, 35) and Szent-Gyorgyi (169), until its full flowering began in the 1950s and 1960s. Biological piezoelectricity was discovered in bone and subsequently found in many tissues (41, 56, 105, 109, 142, 159). These observations led to interest in the sensitivity of cells to electrical signals (6, 108, 110), and numerous studies showed that weak electrical currents (10^{-13} to 10^{-5} A) could cause bone growth in animals and human beings (7, 18, 24, 30, 31, 32, 54, 57, 73, 77, 84, 95, 96, 130, 137, 181, 186, 192, 193, 195). This phenomenon was patented as an effective therapy (174), approved by the Food and Drug Administration (FDA), and is now routinely used clinically for the treatment of bone nonunions and pseudarthroses.

A second approach to the treatment of the same disorders using magnetic fields began in the early 1970s and followed a similar course involving animal studies (8, 39, 140, 141), clinical trials (9), FDA approval, and consequent commercialization and clinical use (160). Electrical treatment procedures are being studied in connection with osteomyelitis (180), ligament healing (52), osteoporosis (10, 43, 86) joint fusion (23), acceleration of normal fracture healing (40, 71, 118), and other applications (74, 75, 78, 81, 85, 135, 168, 176, 177).

The door has been opened to a range of studies, approaches, and potential developments that were simply unimaginable only 20 years ago. Electrical factors have been shown to be intimately involved in the process of regeneration (15, 17, 20, 27, 28, 29, 44, 82, 83, 154, 165, 166), and we now have a hope of being able to restore this capacity in man as has been shown by many studies involving limb regeneration (19, 161, 163) and nerve regeneration

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hazard. Thus, there appear to be no ramifications for long term effects on behavior of animals and humans. However, if this is the case, then what sense are we to make of reports of altered neural function that result from exposure to ELF fields (e.g., suppressed melatonin and SNAT activity in rat pineal gland; efflux of calcium ions from brain cortices; histological change in the cerebellum and hippocampus following perinatal exposure, and so on)? Are these neural effects no more than "noise" to the behaving organism? In the last section of this review (RESEARCH NEEDS), possible reasons for the disparity between cell biology, neurochemistry, and behavior are presented. Based on the hypothesized reasons for the existing disparity, a number of research needs are summarized. These include suggestions for specific experiments.

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(1982) should be repeated with larger sample sizes, and, as indicated above, someone should specifically address whether rabbits exposed prenatally show learning deficits in the acquisition of a classically conditioned motor response.

Finally, there is a need to evaluate populations at risk or populations already compromised by exposure to other agents. In the real world there are subsets of population members that are "at risk". They tend to be more susceptible to secondary stressors. But few, if any, synergy-type studies have been conducted employing ELF fields. There are other research needs, but the above are essential.

SUMMARY AND CONCLUSION

Behavioral responses to ELF electric and magnetic fields are reviewed starting with the simple sensory awareness or detection by an animal and moving on through more complicated behavioral responses such as behavior which averts exposure. The literature selected in this review is taken primarily from the area of behavioral toxicology. As such, it does not review work on specialized response systems to ELF fields. The most notable of these omitted specialized response systems are electroreception, which occurs in a number of fish species, and homing/navigation and communication of the location of food which occurs in several species of birds and in honeybees respectively.

The toxicologic orientation of most researches which evaluate the effects of exposure to ELF electric and magnetic fields has been influenced primarily by the "missions" of the U.S. Department of Energy and the power industry programs to determine the health effects of power frequency (50- and 60-Hz) electric and magnetic fields. Because of these large programmatic efforts most of the research conducted since 1977 has in fact been done at 50 or 60 Hz.

In the context of the above limitations, remarkably few robust behavioral effects have been reported. Those that have been reported probably relate to an animal's perception of the electric field, although there are some exceptions to this generalization.

The apparent lack of consistent deleterious effects in animals is consistent with recent studies on humans that have been conducted in the UK. With this in mind, it is tempting to conclude that exposure to an ELF field is a rather innocuous event and, other than possible mini-shocks, without

of the cerebellum are the substrate of memory for a simple learned motor habit in the rabbit. With this in mind, and in light of Hansson's observations (1981, 1985) of histological change in the rat cerebellum (which include the dentate and interpositus nuclei), an appropriate experiment to evaluate the functional/behavioral significance of Hansson's finding would be to prenatally expose rabbits to ELF fields as Hansson has done and then, when the progeny are adults, test them for conditioned leg flexion or the nictitating membrane response as Thompson has done. To date, no one has done this experiment nor have they proposed to do it.

One of the most frequent questions asked of Adey and Blackman is "What is the functional significance of your observations of efflux of calcium ions from cortices exposed in vitro?" To answer that, behaviorally, we need again to establish what linkages exist between subtle changes in intraneuronic calcium pools and behavior. One answer to that question is elegantly detailed by Lynch and Baudry (1984). Calcium ion infusion into the subsynaptic space is requisite for "cortical" memories to be formed. Events, other than exposure to ELF fields, which perturb the normal calcium ion influx into the subsynaptic space disrupt behavioral indices of memory (e.g., rodent memory in a radial maze), as well as electrophysiological events that are taken as models of memorial processes, e.g., long term potentiation (LTP) in the hippocampus. So, here again, because some rules of correspondence are in place, the physiological psychologist has some idea of what questions to ask under ELF exposure conditions approximating those in which Adey (1985) and Blackman (1985) obtain their calcium ion effects. But, what behavioral scientist has studied radial maze memory during exposure to an ELF field; similarly who has evaluated LTP (which can be done in vitro) under ELF exposure conditions that approximate those of Adey and Blackman?

Beyond the approaches detailed above, there are a number of other researches that need to be carried out. The data base for neurobehavioral teratology is inadequate. It is especially inadequate given suggestions in the literature that ELF electric and magnetic fields may be potent teratogens (Sikov et al. 1984). There are a number of postnatal parameters that have yet to be assessed following prenatal exposure to ELF fields. Among these are learning and memory, sensory processes, and analgesia. The activity assessments reported by Lovely, Creim, and Phillips (1984a, 1984c) and Frey

One would be more concerned with such findings at 50 μA summed-current injected.

RESEARCH NEEDS

If we exclude the specialized response systems that have evolved in some species (e.g., electroreception, homing, and navigation), it is tempting to conclude that remarkably little, if any, behavior is radically altered by exposure to ELF fields. What then are we to make of Hansson's findings (1981, 1985) that prenatal exposure to 50-Hz electric fields leads to a number of histological anomalies in the rabbit cerebellum, and the Albert et al. observations (1984) of similar exposure-dependent changes in the rat's cerebellum and hippocampus? What are we to make of Wilson et al. (1981) who report that one month of exposure to 60-Hz electric fields at 65 kV/m suppresses nocturnal melatonin levels and SNAT activity in the pineal gland of rats? The pineal observations have been subsequently obtained at field strengths as low as 1.9 kV/m (Anderson, pers. com. 1983). And what are we to make of the efflux of calcium ions that occurs in chick, cat, and rat cortices when these tissues are exposed in vitro to RF fields modulated at particular ELF frequencies (Adey 1985; Blackman 1985). If these neural alterations occur in the same animals tested in behavioral experiments, then why has so remarkedly little been found? Are these neural effects just "noise" to a behaving organism? Or, are there other possible explanations for the lack of concordance? One possible answer to this question relates to the very substance of behavioral neuroscience and physiological psychology.

The primary objective of the physiological psychologist is to identify the rules of correspondence that are the linkages between the simple elements in the nervous system (neurons, glia, transmitters, receptor types, etc., and their general organization) and behavior. These rules of correspondence are not yet well understood, and as a result it is difficult for behavioral scientists to know whether s/he is asking the right question of their animal or even using the right species and behavioral preparation. In a few cases some of the rules of correspondence are being worked out, and the astute behavioral scientists should apply these to evaluate the putative toxicity of ELF fields. An example or two should suffice to make the point. Thompson (1983) has provided unequivocal evidence that the dentate/interpositus nuclei

experienced by human subjects and relate these values to the subjects' physical and psychological well-being. In the first of two study types, nearly 400 occupationally exposed personnel completed a widely used health-questionnaire interview (Broadbent and Gath 1979; Crown and Crisp 1966 1979). Estimates of exposure to 50-Hz electric and magnetic fields were obtained; and, on nearly 300 of the 400 workers, actual measurements over a two-week period were also obtained. The results were unequivocal. First, estimates of exposure tended to exceed actual measured exposure (measured mean of 30.5 kV/m-h/2 wk). Second, no significant correlations between either estimated exposure or actual exposure and health status was found. The study is statistically sound and was conducted blind.

In a second type of study, 76 healthy human volunteer subjects had electrodes placed over 10 locations on the upper body whereby a total of 500 μA at 50 Hz could be "injected" into the subjects. The decision to inject current was in deference to possible effects of hair stimulation (and resulting perception) that would occur if subjects were actually exposed to 50-Hz electric fields. The authors estimate that the summed-current injected was equivalent to that which might result from a grounded man standing in a 35 kV/m field. The subjects were tested over two sessions with half the subjects receiving injected current the first session, and half receiving it in the second session. The four major tests the subjects took under both conditions were: syntactic reasoning, semantic reasoning, visual search, and serial reaction time. Stress/arousal levels were also determined using a mood adjective check list at the start and end of each session. The study was conducted double-blind. Two significant differences were found. The first was a significant shift in the ability to determine truth of sentences. However the results make it impossible to determine if the effect of injected current is to improve learning in the first session or impair performance in the second session (or impaired performance generally). Nevertheless the interaction is an interesting one. The second and similarly ordered-effect relates to the self-report of arousal; it emerged as a significant interaction effect: arousal falls from the start to the end of a session; but it falls less for the current-off group only in the se^ond session. Even though these are rather minimal effects, it is unfortunate that other "dose" groups were not included (i.e., 500 μA, albeit distributed, is a fair amount of current).

fields at 65 kV/m, and found no significant effects of exposure. The study is well-designed and the evoked-potential data appear to be appropriately analyzed.

Hansson (1981) exposed rabbits to a 50-Hz, 14 kV/m electric field throughout gestation and through 7.5 weeks postnatally. He found a number of histological changes in the cerebellar Purkinje cells of his exposed rabbits. There included a reduction in the size and number of Nissl bodies, a reduction in the rough endoplasmic reticulum, and the appearance of lamellar bodies. There were also significant reductions in the body weights of his exposed rabbits suggesting more general deleterious effects of exposure or possible other stressors in his exposure environment. However, in subsequent experiments where the exposed subjects appeared to be generally healthy and better maintained (Hansson 1985), similar findings were reported as a result of perinatal exposure to electric fields. In a different laboratory Albert et al. (1984) has also observed the appearance of lamellar bodies both in cerebellar Purkinje cells and hippocampal pyramidal cells as a result of prenatal exposure to a 60-Hz electric field at 60 kV/m. The effect was obtained in rats. So, despite reservations about the exposure environment in Hansson's initial study (1981), this may be a genuine neurohistological change due to perinatal exposure to ELF fields. Whether these alterations portend pathology is not year clear (see RESEARCH NEEDS).

Behavioral Effects in Humans

Although Russian investigators have reported that workers exposed to 50-Hz electric fields in switchyards suffer from a number of neurovegetative disorders (e.g., Asanova and Rakov 1966; Filippov 1972; Korobkova et al. 1972), it is difficult to evaluate these reports because there is no real measurement of the fields to which the workers were exposed; nor is there a meaningful estimate of the duration of exposure. Had a rigorous dosimetric investigation been conducted, it might just as well turn out that these effects result from mini-shocks and not from exposure to ELF fields per se. Changes in neurovegetative function might be more understandable if they had come from mini-shocks.

More recently however, a series of studies (Norris, Male, and Bonnell 1985) have been reported that document in detail the fields or currents

littermates were tested in three tasks: shuttlebox avoidance, a residential maze (which assesses exploration and activity), and the preference/aversion task described by Hjeresen et al. (1980). They found that the perinatal exposure to a 60-Hz electric field vs. sham-exposure failed to statistically differentiate groups in any of the tasks employed. There are two shortcomings of this study. First, the sample sizes (n = 10 subjects per subgroup) is a little small for a behavioral teratology study. This is especially unfortunate because a number of consistent trends in this study's data are suggestive of an effect of exposure on female progeny. Second, the range of behaviors examined is not a very complete assessment for postnatal neural alteration (e.g., no sensory or motor tests, no memory tests, no analgesia tests, and so on).

In another study (Lovely, Creim, and Phillips 1982, 1984a), postnatal behavioral tests were carried out on F_2 generation Hanford Miniature Swine that had been exposed prenatally to a 60-Hz, 30 kV/m, electric field. The assessments included a test for neuromuscular development at 3 days of age (righting and negative geotaxis); a test for open field activity, vocalizations, orienting response/habituation at 1, 3, and 5 weeks of age; and learning/memory in a multi-choice T-maze at 8, 12, and 16 weeks of age. There were no statistically significant differences between exposed and sham-exposed swine in the neuromuscular tests (although there were some animals failing to respond in the exposed group). Similarly, there were no significant differences in the T-maze tests for learning and memory (parameters assessed included startbox latency, goalbox speed, errors made, trials to criterion or completed/30-min test). However, in the open field, the exposed females made significantly less vocalizations, both within and across all 15-min test sessions. The same females were also less active in the test at one week of age. The nature of the overall design precluded cross-fostering at parturition, so we do not know whether the effect is the result of prenatal exposure, postnatal exposure, or altered mothering. We do know that the mothers of these swine showed anomalous reproductive behavior prior to conception and farrowing (Sikov et al. 1984).

Neural functions other than behavior have been evaluated following prenatal exposure to ELF fields. Jaffe et al. (1983) monitored the ontogeny of the visual-evoked response in rats prenatally exposed to 60-Hz electric

Lott and McCain (100), at North Texas State University, applied an electric field of 40 V/m at 640 Hz to rats; they found a significant increase in brain electrical activity during the 1-h exposure period. Similar changes in brain activity can occur at higher frequencies (36, 37, 49, 158, 194).

Fischer and colleagues at Graz University in Austria exposed rats to 5,300 V/m at 50 Hz for periods ranging from 15 min to 21 days (51). They found that the level of norepinephrine in the brain was significantly affected after as brief an exposure as 15 min. The norepinephrine level first rose above normal, then, by the 10th day of exposure, fell below normal. Similar results were reported following exposure to 50 to 500 microwatts/cm^2 at 2.4 GHz (64).

Noval et al. (131), at the Naval Research Laboratory in Warminister, Pennsylvania, and Bawin and Adey (14), at UCLA, each reported effects of ELF fields on brain metabolism. Noval's group exposed rats to 0.5 to 100 V/m at 45 Hz for 30 to 40 days and found decreased levels of brain choline acetyltransferase. Bawin's group reported that the exposure of chick and cat brain tissue to 5 to 100 V/m at 1 to 75 Hz for 20 min altered the tissue's binding of calcium. Hansson reported histopathological changes in rabbit brain following chronic exposure to ELF electric fields (69), and we have recently confirmed these observations in mice (70).

Friedman, Becker, and Bachman (55) at the Syracuse Veterans Administration Medical Center; Gibson and Moroney (60) at the Naval Aerospace Medical Research Laboratory; Hamer (67) at UCLA, Konig (90) at Technical University in Munich; and Persinger, Lafreniere, and Mainprize (139) at Laurentian University in Ontario, each reported a significant effect of ELF fields on the reaction time of human beings or monkeys. An effect of such fields on animal activity was reported by Moos (124) of the University of Illinois.

Neuroendocrine System

A variety of statistically significant effects, including depressed body weight, depressed water consumption, increased adrenal and pituitary weights, and altered serum levels of albumin and hydroxycorticosterone were found in rats exposed to 15,000 V/m for 1 month (112). The results indicated that exposure to the field produced a physiological stress response. Noval et al. (131) independently performed similar experiments at much lower field

strengths and reached essentially the same conclusion. Magnetic fields produced a similar response (20).

Mathewson et al. (120), at the Armed Forces Radiobiology Institute, exposed rats for 28 days to 0.5 to 100 V/m at 45 Hz. Their data revealed a variety of statistically significant effects in the exposed animals, which included changes in blood glucose, hemoglobin and hematocrit, total lipids, triglycerides, and body weight (112).

Mathewson's study (120) tended to confirm the Noval et al. results, with the chief difference being the severity of the effects. This led to an attempt to delineate the differences in the conditions under which the studies were performed.

The Noval et al. study was performed inside a Faraday cage formed by the steel-wall construction of the facility at which the test and control animals were housed. The possible significance of the shielding was not recognized in the beginning, and it was, therefore, not incorporated into the design of the Mathewson study. To the extent that Faraday shielding can, of itself, produce biological changes, the shielding can account for the differences between the two studies. Such effects due to shielding have been found in human beings, guinea pigs, and mice.

In the most thorough study of the phenomenon, Wever (185a), at the Max Planck Institute in Germany, isolated volunteers in underground bunkers for 3 to 8 weeks and measured the daily periods of their body temperature and activity rhythms. He found that subjects that lived in a shielded bunker exhibited rhythms whose period was different from those of subjects living in the nonshielded bunker. He also reported that desynchronization--the rhythms no longer rising and falling together--occurred only in the subjects in the shielded bunker. Both effects ceased when Wever applied 2.5 V/m at 10 Hz; this indicated that both the normal electromagnetic environment and the ELF field had a similar influence on the human rhythms studied. Altman and Soltau (1), at the University of Saarbrucken in Germany, exposed guinea pigs to 240 V/m at 10 Hz and maintained parallel groups under Faraday conditions and under normal conditions (no field and no shielding respectively). They found that the shielding produced changes in the blood proteins compared to the normal conditions and that the ELF field caused these changes to disappear. Lang (93), also at the University of Saarbrucken, exposed mice to 3,500 V/m at

10 Hz and maintained parallel groups under Faraday and normal conditions. The shielding produced changes in body water content, hemoglobin, and blood sodium levels; the effects were eliminated by ELF fields.

Prokhvatilo (146), at the Mareyev Institute in Kiev, conducted experiments on the effects of 50-Hz electric fields of 1,000 to 5,000 V/m on the neuroendocrine system of rats. He found that after several months exposure iodine metabolism in the thyroid and ketosteroid metabolism in the adrenal gland were both altered. In addition, the microscopic appearance of the thyroid also changed because of the electric field. Similar effects on the alteration of thyroid function were reported by Dumanskii, Popovich, and Prokhvatilo (50), of the Kiev Scientific Research Institute; they also found a decrease in blood cholinesterase activity in the field-exposed rats.

Blood

Studies have demonstrated effects of ELF electric fields on the cells and other constituents of blood (29, 62, 107).

Cardiovascular Systems

Gann (58), at Johns Hopkins University, subjected dogs to a small controlled hemorrhage and examined the effects of 15,000 V/m at 60 Hz for 5 h on the dogs physiological response to the hemorrhage; he found that the blood pressure and heart rate were significantly different in the exposed dogs as compared to the controls (which also experienced the hemorrhage). Fischer, Waibel, and Richter (50a), at Graz University in Austria, found that brief exposure of rats to 5,300 V/m, 50 Hz, caused a significant drop in heart rate.

Beischer, Grissett, and Mitchell (21), at the Naval Aerospace Medical Research Laboratory, exposed volunteers to a magnetic field of 1 G at 45 Hz for 1 day; in 9 of the 10 subjects they observed a significant increase in the level of blood triglycerides following the exposure.

General Physiology

ELF electric fields have been reported to alter the rate of cell division in mice (106), alter the metabolism of rat sperm cells (3), affect muscle metabolism in rats (143), and slow the rate of tumor growth in mice (11).

Analysis

The reports described above may be summarized this way:

1. EMFs can alter the metabolism of all body systems, including the nervous, endocrine, cardiovascular, hematological, immune-response, and reproductive systems.

2. The effects on each tissue or system are largely independent of EMF frequency.

3. An organism's response to an EMF is determined in part by its physiological history and genetic predisposition; individual animals, even in an apparently homogeneous population, may exhibit changes in opposite directions in a dependent biological parameter.

4. EMF-induced biological effects are best characterized as adaptive or compensatory; they present the organism with an environmental factor to which it must accommodate.

If attention were restricted to EMF-related changes in individual body systems such as the brain or blood, it might be hypothesized that the action of the field involved certain enzymes, specific antibody regions of certain cells or particular organs. But the studies clearly showed that EMFs produce a complex interrelated series of physiological changes (Figure 1). It follows that the consequences of EMF exposure must be understood in terms of an integrative response of the entire organism. In my view, after the EMF is detected, information concerning it is communicated to the central nervous system which then activates the broad array of physiological mechanisms that are available to furnish a compensatory response. As is generally true of an adaptive response, the particular biological system that is invoked, and the nature of its response, will depend on numerous factors including the animal's internal conditioning and its external environment. The biological processes that follow detection of an EMF are similar to those associated with the response to any biological stressor. Thus, for example, the cellular or molecular mechanisms that operate in the adrenal following a cold stress to produce altered serum corticoid levels also operate following an electromagnetic stress, because adrenal activity is initiated by neuronal and hormonal signals, not by the actual presence of the stressor agent in the tissue.

If electric and magnetic fields are simply nonspecific biological stressors that can elicit a systemic adaptive response in the exposed organism, what kinds of effects will occur in exposed human beings? If an

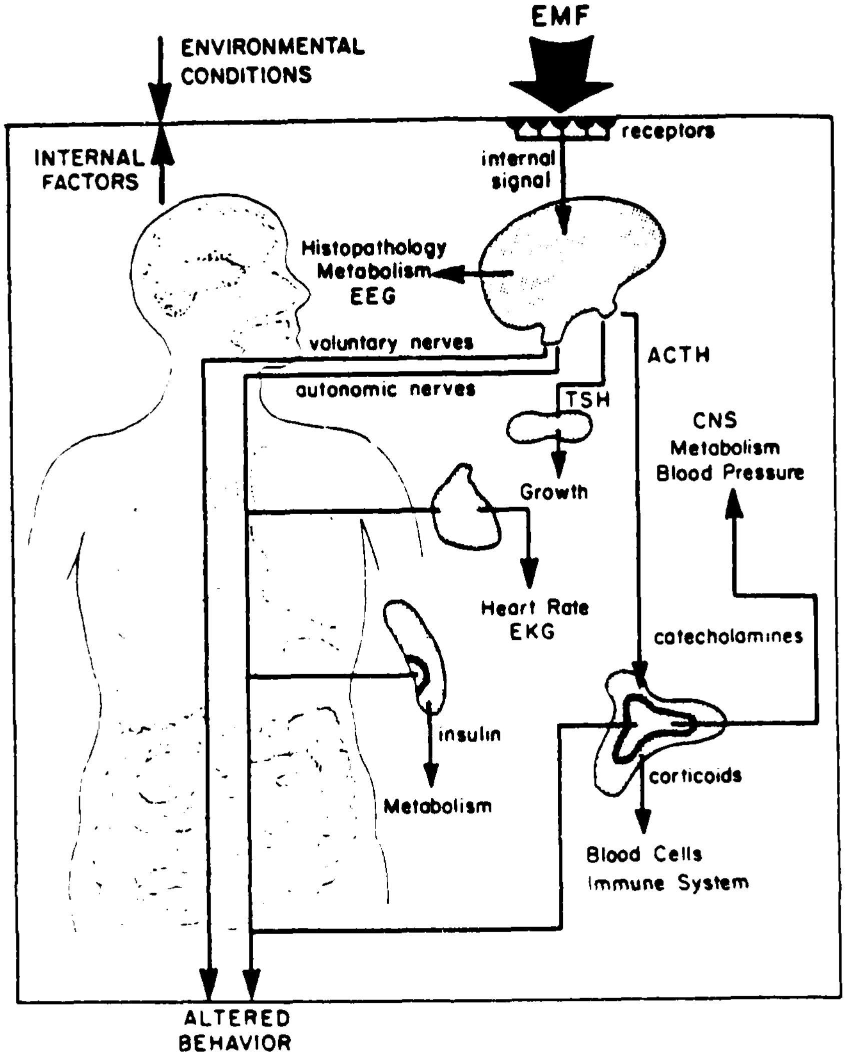

FIGURE 1

The physiological effects of applied electromagnetic fields.

organism is subjected to, for example, a cold stress, adaptive changes occur. If the stress is maintained, the animal's defenses break down, resulting in a diagnosable disease. But there is no signature disease for a cold stress. The animal could exhibit any of several diseases; infection (if a viral or bacterial agent were present in the environment) and pneumonia (if its respiratory system were already weakened for other reasons) are examples. The effects produced by environmental EMFs will depend on comparably diverse factors, and therefore will be manifested by an increase in all diseases.

In the example of the animal undergoing a cold stress, suppose that a second stress is applied (for example, that the animal is forced to live in cramped quarters). The expected result in an animal undergoing two stresses is that, whatever disease it is fated to develop when stressed beyond its limit, it will manifest that disease more quickly than if it experienced only one stressor. Thus, in general, EMFs will be a contributing factor, but not a strict cause, of disease.

If environmental EMFs are biological stressors, then epidemiological studies should show a correlation between EMF exposure and the incidence of disease. Many epidemiological studies have found this correlation (42, 89, 97, 98, 103, 123, 129, 138, 172, 175, 184, 185, 191).

HEALTH RISK OF SANGUINE/SEAFARER

The evidence shows that manmade EMFs are etiological factors in human disease. Many studies can be related to the health risk of high-voltage powerlines and it is possible to delineate zones of relative risk in their vicinity. But Sanguine/Seafarer electric and magnetic fields are significantly smaller than the corresponding fields of high-voltage powerlines, and the only indisputable method of evaluating the risk of Sanguine/Seafarer fields is to conduct biological experiments involving exposure to simulated Sanguine-strength fields as was recommended in 1973 (145).

Scientific studies will be needed if the environmental impact of Sanguine/Seafarer is to be rationally determined. Such studies should also address the potential global impact of Sanguine radiation in the magnetosphere. Helliwell had detected 60-Hz radiation in the magnetosphere from high-voltage powerlines (134). The radiated energy is amplified in the magnetosphere via an electron-wave interaction in which electrons precessing about the earth's field lines surrender energy to the electromagnetic wave. Sanguine/Seafarer, unlike powerlines, is intended to radiate and the physical and biological consequences, if any, of the Helliwell phenomenon as induced by Sanguine/Seafarer should be ascertained.

MECHANISMS OF DECISION

If our desire is to actually know the truth, what is the best way to

evaluate the public health risk of Sanguine/Seafarer? The accumulated lessons gained in previous Federal level attempts to consider potential health dangers of exposure to environmental manmade EMFs provide the answer.

Shortly after the end of World War II, the Tri-Service program was initiated to determine safe exposure limits to EMFs. The concept of safety that evolved was based on the results of acute experiments: If a test animal's body was not overheated then (with a small safety margin) the corresponding EMF level was considered safe. Harm was equated to cooking, and safety to non-cooking. The decisions in the Tri-Service program were made by industry and the DOD.

About 10 years after Tri-Service, the Soviet Union began irradiating the American Embassy in Moscow with a microwave beam of 2 to 18 microwatts/cm^2, a level approximately 5,000 times below the safe level of Tri-Service. For approximately 7 years the government studied the exposed workers for unusual disease incidences, and conducted microscopic studies of blood smears from embassy personnel looking for possible chromosomal aberrations. Sometime in the middle or late 1960s, a research program called Project Pandora was begun to complement these observations. The data from Pandora was destroyed without being published. The employees of the embassy were irradiated unknowingly, and had no opportunity to withdraw from the beam, nor to probe the expertise or impartiality of the people running the bioeffects studies.

In the late 1960s Sanguine/Seafarer was proposed and studies of the biological effects associated with the proposed antenna were funded by the Navy. The review group for the data thus obtained was a blue-ribbon panel (BRP) chosen by the Navy which met in December 1973 to consider the evidence. The BRP recommended continued and expanded research efforts (145). Despite this, most research was ended around 1975 when the Navy pronounced the antenna safe and pressed for its construction.

Within months of the public release of the BRP report (on the Senate floor) a second BRP was appointed at the behest of the Navy by the president of the National Academy of Sciences (NAS-BRP). The final report of the NAS-BRP tracked closely in form, content, and technique of analysis, as well as the testimony given by several panel members on behalf of the electric power industry in health and safety hearings concerning 765,000-V powerlines

then being considered for construction in New York (26, 155).

The question to both the BRP and the NAS-BRP was nonspecific ("is it safe "). In both cases the Navy, or someone acting on its behalf, was the sole determiner of the expertise and credibility of the panel members. None of the panel members of either committee were ever tested regarding the bases of their views.

What does the history teach? First, that the naked conclusion of a blue-ribbon panel has no force of logic, claim to truth, or compelling reason to assent to its findings. Its conclusion merely reflects the unexposed bias and interests of its members. Blue-ribbon panels will be ignored by adversely affected parties, just as the Navy ignored the BRP, and others ignored the NAS-BRP. Second, there must be concrete issues for the scientists to consider. No one has urged that there is no risk from Sanguine/Seafarer, so it cannot be completely safe. Since the BRPs were not given concrete issues, they simply picked their own issues, and these bore no particular relation to the true societal problem. Third, the issues--once they are defined--will obviously be adversarial and cannot be settled by consensus. The Navy clearly wants the antenna and it supports the scientists who posit the notion that Sanguine/Seafarer will be safe. Some scientists disagree with this notion. The people who live in Wisconsin and Michigan who will actually be running the risk of exposure, whatever it will be, constitute still another interest group. The relations among these four groups are inherently adversarial.

There is a better way. The process must begin with a framing of issues, because there must be agreement on what actually constitutes the problem under discussion. Equally important is the direct involvement, or opportunity for involvement, of the people who would be impacted. They have a right to be heard. With issues and parties-in-interest, scientific talent must be made available to both sides, not one side as has been the case in most instances. The experts could then agree on the choice of judges, procedure, rules of evidence, and then the issues would be judged in the sunshine. Each witness could be specifically questioned by his adversary. This concept, the science court (121, 122, 171), follows the same principles and practices for the determination of truth and the pursuit of justice as are practiced in all other spheres in our society.

SUMMARY AND CONCLUSION

EMFs are in clinical use in many areas including the treatment of bone disorders, pain, and infection. Acceleration of the tempo of normal healing, and induction of regeneration in limbs and nerve have been demonstrated in animals following application of EMFs. A broad range of organisms from bacteria to vertebrates have been shown to detect and respond to EMFs. But not all biological responses to EMFs are therapeutic or otherwise beneficial. Numerous animal studies have shown that EMFs can elicit an adaptive syndrome--the stress response--mediated by the neuroendocrine system. Since the chronic application of any stressor can be inimical to health because it taxes adaptive capacity, it follows that chronic exposure to EMFs will be a risk to health. Consequently, EMF-exposed people will exhibit higher incidences of all diseases, not only higher cancer levels as have been reported.

The association between risk and the EMFs produced by specific emitters depends on the actual EMF level. For high-voltage powerlines the association is clear, but for Sanguine/Seafarer it cannot be rationally determined on the basis of the present evidence. The evidence that is needed is obvious (145).

An adequate assessment of the health risks of Sanguine/Seafarer cannot emerge from the present process.

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e., exposure to the EF at some time during the 14 days prior to amination. With this questionable criterion for "acute" exposure the rformance in the psychological tests was found to be lower among the "acute" posed as compared with the "nonacute" exposed. No other results indicated e presence of an "acute" effect. It should nevertheless be pointed out that y "acute" effect might be ascribed to other aspects of work in substations, g., stress, awareness of risks of accidents; discomfort caused by, and fear , spark discharges or shock; etc.

Differences in the ratio of male and female offspring between exposed and nexposed populations were mentioned by both Knave et al. (1979) and Roberge 976), although in neither case did the authors ascribe any significance to em. The trends were in opposite directions in the two surveys and in the se of Knave et al. (1979) were known to have begun before the subjects arted work in the substation.

Nordstrom and Birke (1979) described preliminary studies in which eight ses of congenital deformity were found among 113 children of men who worked 400-kV substations at the time of conception. Only 2.6% of nonexposed rkers' children showed such deformities. In addition, chromosome analyses eight of the workers showed a trend toward increased frequency of breakage.

Nordstrom et al. (1981) analyzed the pregnancy outcome of the spouses of le substation workers and found an increased frequency of congenital lformations. Exposure data, however, went back 40 years, and part of the ntrol group was the exposed workers at a younger age. The authors phasized that their results must be interpreted with caution and that rther research was needed to clarify any health hazards. Chromosome errations were also studied in 20 workers and compared to 20 selected ferents for clinical standard material. More chromatid gaps and chromosome eaks were noted among the substation workers. Again, the authors pointed to e necessity of caution in any interpretations mainly because of the limited mber of persons examined and the special character of control material. romosome analyses from an earlier study were used for 5 control subjects. us, different technicians could have been involved possibly introducing a oring bias. In addition no information is given on electric and magnetic eld exposure, nor are any statistical analyses provided. Consequently no ferences can properly be drawn from this report.

ram (EEG); electrocardiogram (ECG); blood biochemistry including tests of iver function, serum electrolytes; and complete physical and psychological ssessment with psychometric and personality tests. At the time of xamination the subjects were not identified as being exposed or control. The xposed group consisted of:

(a) 19 lineman with an exposure experience calculated to be 7-kV/m h/day - up to 8,000-kV/m h over ten years, and

(b) 11 substation workers with an average calculated exposure of 13-kV/m h/day - up to 36,000-kV/m h over ten years.

It was concluded from this study that extra-high voltage (EHV) work does ot cause chronic ill health in substation staff in Ontario.

In 1974, the Swedish State Power Board started physiological, sychological, and physical investigations on the effects of electric fields EF) on personnel in Swedish EHV substations. In this study, 53 subjects who orked more than five years in 400-kV substations were examined and compared ith a matched control group of 53 nonexposed workers from the same power ompanies (Knave et al. 1979). Matching considered age, geographical location nd length of employment. It was determined that some substations ("higher") ad large areas with field intensities up to 10 to 15 kV/m while others "low-built") may have substantial areas with field intensities of about 20 V/m. The aim of the study was to determine if there were any persistent, hronic health effects in the exposed group as a consequence of exposure. xamination included the nervous system for neurological symptoms, blood ressure, ECG, and complete blood count. The results indicated no differences etween the exposed and control groups as a consequence of long-term exposure o the EF. The groups differed, however, in that the exposed group had (a) onsistently better results in psychological performance tests; (b) fewer umber of children, especially boys; and (c) somewhat higher education. The ifferences in test results were apparently a reflection of the higher ducational level among the exposed individuals. The difference in number of hildren was also thought to be related to factors other than exposure since his difference was found to be present 10 to 15 years prior to employment in 00-kV substations.

Attempts were also made to elucidate any "acute" effects of exposure,

Influence of Power Frequency Electric and
Magnetic Fields on Human Health*

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INTRODUCTION

Recently, public concern has been expressed about possible risks to human health, function, and well-being arising from exposure to the electric and magnetic fields associated with overhead transmission lines. Several studies have been performed to determine whether exposure to electric or magnetic fields with power frequencies of 50 or 60 Hz constitutes a health hazard. The study populations have included electric utility personnel, workers in other industries with electric or magnetic environments and residences at varying proximities to distribution lines. Systematic studies to determine the effects of electric fields on linemen and substation workers have been conducted in the United States and Sweden. Occupational studies have also been reported from Canada, France, and the United Kingdom. The reports from Soviet and other East European countries, based on substation personnel present serious difficulties in methodology and interpretation. These studies have been reviewed by Michaelson (1979) and Mehn (1979). Only those reports of the last five years are the subject of this review.

OCCUPATIONAL EXPOSURES

A study was reported by Stopps and Janischewskyj (1979) in which 30 high voltage maintenance men from Ontario Hydro, together with 30 other employees matched for age and educational level but not exposed to electric fields, received clinical examinations. The investigation included electroencephalo-

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Bauchinger et al. (1981) repeated the chromosome studies on German substation workers. Chromosome analyses were done in lymphocytes of 32 workers occupationally exposed for more than 20 years in 380-kV switchyards. As compared with a control group of 22 workers of similar age and occupation but without field exposure, there was no increase in structural chromosome changes. Furthermore, no increase in abnormal pregnancy outcome could be demonstrated in epidemiological studies on the German substation workers (Hauf 1981).

In another study, Nordstrom et al. (1983) addressed the potential relation which may exist between pregnancy outcome and the occupation of the father exposed to different electrical voltages. The population of the study included 372 couples in which the male worked at a given time for the electrical industry of Sweden. The analysis included 480 pregnancies among these couples.

The exposure was estimated from questionnaires distributed to workers. According to their responses, the workers were grouped into 3 subgroups (less than 70 kV, 130 to 200 kV, 400 kV). They were also grouped into occupational groups (high voltage switchyard, construction or repair of switchyard, other tasks).

Questions on the following were presented: miscarriages, birth defects, stillbirths, and fertility problems. The authors related these problems to many variables without really controlling for them.

A decrease in the number of normal pregnancies especially as a result of birth defects was indicated for fathers who worked in contact with high electrical voltage.

In their discussion, the authors attribute these changes to the fact that "The employees' bodies and/or objects in the switchyards are electrically charged and then discharged..." They stress also that the presence of chromosomal aberration in these workers could be associated with the observed problems.

There are a great number of weaknesses in this study. Exposure was measured according to a questionnaire sent by mail to the subjects. It is not certain that the questionnaire discriminates in a valid manner between the "exposed" and "nonexposed" men. The regrouping of the exposure by different voltages and by occupational groups is not clear. The observation of problems of pregnancies by occupational groups cannot be attributed to the exposures to

different voltages since within each occupational group there are exposed and nonexposed people. The number of subjects on which the authors base their analysis are very small.

Thus, the problems of the epidemiological design and the statistical analysis are so serious that the conclusions of this study cannot be accepted. The same criticism relates to the measurements of exposure and the attribution to each individual of a level of exposure.

The main problem in retrospective cohort studies relates to the insufficiency in documentation of the different exposure factors and relevant confounders. For instance, in the Swedish study on fertility and reproduction outcome among substation workers (Nordstrom et al. 1981), subjective exposure data go back 40 years in time. It is almost impossible under such corditions to reconstruct the relationships of exposure to electromagnetic fields or known genotoxic factors at the time of conception of the first child. In this type of epidemiological study there is a definite need for knowledge of individual exposure data. Before we have that, no reliable conclusions can be drawn.

Letters to the Editor

Recently several investigators have suggested relationships between the appearance of leukemia and certain occupational classifications. Milham (1982) suggested that 10 of 11 occupations with potential exposure to electrical and magnetic fields have a raised proportionate mortality ratio (PMR) for leukemia. This excess is statistically significant for the following occupations: "electricians, power station operators, aluminum workers."

The observations were extracted from a study of much greater scope where the author examined the mortality for total deaths among men between 1950 and 1979 (438,000 deaths) in the State of Washington. The observed illnesses are grouped according to leukemias and acute leukemias. The analytical technique used is the PMR.

Milham (1982) related 11 industries to "exposure to electrical or magnetic fields" and computed a proportionate mortality rate as a ratio of actual deaths per industry to expected deaths per industry from cancer. He stated he was unaware of obvious leukemogenic agents in the occupations, and therefore

his findings suggested that "electrical and magnetic fields may cause leukemia." His calculated PMRs were 137 for all leukemias and 163 for acute leukemias in the 11 industries. In his discussion, the author concluded that this observation suggests that the electrical and magnetic fields may cause leukemia.

Milham considered no other possible causes of cancer than electromagnetic fields in reaching his conclusion, and offered no explanation for ignoring other possible causes except a lack of awareness of "obvious leukemogenic exposures" in the listed industries. He also ignored the possibility of nonoccupational factors such as smoking and differences in life-style, and does not provide any information on ages at death. The numbers of deaths over a 20-year period (136), or about 7 per year, in the state seem low as a basis for such a sweeping conclusion. Questions can also be raised regarding the accuracy of the diagnosis of leukemia on the death certificate, particularly over the time period 1950 to 1979, when there were improvements in medical care and consequently in methods of diagnosis.

The observations reported here were extracted from an analysis of a much greater scope. The PMR for a cause of death may be raised simply because there is a decrease in other causes of death among a group of workers. The author does not indicate the constraint he utilized for each occupational group. What constitutes, for example, the occupation "electrical engineers?" "Electrical technicians?" Does this include the persons really exposed to magnetic and electrical fields? The authors does not tell us if the occupational classes correspond to the last occupation or to the principal occupation of the individual during his life.

In his conclusion, Milham indicated his results may signify that electrical and magnetic fields cause leukemia. This remark clearly goes beyond the strength the study possesses. A letter to the editor does not ordinarily become an object of peer scientific review. It is necessary then to be judicious in the interpretation of these results. At best, Milham's views are highly speculative.

Wright, Peters, and Mack (1982) listed the proportional incidence ratios (PIRs) for leukemia, acute leukemia, and acute myeloid leukemia among white males in Los Angeles from 1972 to 1979 for 11 electrical occupations (occupation at time of diagnosis). The occupational categories where the same

as used by Milham (1982). The number of cases were zero in two categories, one in three categories and 6 or less in all other categories except one (electricians). The particular type of analysis used proportional incidence rate was obtained by comparing the reports of the proportion of exposed workers among the total of other cases of cancer reported in this register.

The authors suggested there is a link between the incidence of leukemia and work in certain occupations where there may be exposure to electric and magnetic fields. This is particularly the case for "power linemen" and "telephone linemen." In their discussion, the authors noted that it is not the electric or the magnetic field itself which is responsible for this excess, but that it may be related to another unmeasured factor which was common in the exposed occupational groups.

This report provides no data except a table listing cases of leukemia for the eleven occupations over a period of seven years. While the occupations are related to electrical systems only, the absence of other data and lack of analysis suggest the findings are entirely speculative.

There are several weak points in this study. The first involves the small numbers. The excess of acute myeloid leukemia in "power linemen" and the "telephone linemen" is based on observation of only two cases. There are also reservations about the statistical analysis used. PIR is a recent method which, although theoretically correct, has not yet stood the test of time.

In a third report, McDowall (1983) examined the alleged link between mortality from leukemia and exposure to magnetic and electric fields in the workplace. The author produced in reality 2 types of studies, one study of mortality (PMR) and a case study.

Somewhat in the fashion of Milham, McDowall computed proportionate mortality rates for cancer deaths in 10 electrical industries for males aged 14 to 74 for the years 1972 to 74. The industrial categories were, however, somewhat different than Milham's categorization. Unlike Milham's calculations, McDowall did not find a significantly high PMR for the 85 deaths in the ten industries. Some occupations were included erroneously in his occupational categories, and the data are therefore biased.

McDowall also computed the relative risk of death by cancer for a different categorization of electrical industries, using the number of deaths from cancer (537) in males in England and Wales in 1973 as "cases." He

selected 1074 controls from remaining deaths for that year. He matched his controls with the cases within 5-year age groups. He does not describe how these data were used to compute relative risk (RR). He stated his data for 1973 generally support Milham (1982) and Wright, Peters, and Mack (1982), but noted that other causative factors cannot be ignored.

In the PMR analysis the author observed 85 cases of leukemia. The PMR is not in excess for all the occupations. It is in excess for 4 of them, "electrical engineers" (including 3 subclassifications) and "telegraph radio operators." The author also noted 36 cases of acute myeloid leukemia. The relative risk is significantly elevated for all occupations in the electrical industry.

In his discussion, the author concluded that these observations served to reinforce the previous observations made in the American studies. He stressed (by contrast) that there are some differences between the studies. While the Americans found an excess for all the occupations where there would be exposure to magnetic and electric fields, McDowall found some excess for the professional (lower/sub) classes only. He attributed this difference to the mobility of workers between occupations.

McDowall recognized that many factors in an industrial environment may cause death by cancer and did not emphatically suggest electromagnetic fields may be among those factors. He did not provide sufficient information to clarify his tabular data, nor discuss his results in any detail. It is not known if the author speaks here of the principal occupation or the last reported occupation. For each specific occupation, the numbers are small. Any conclusions based on his findings would therefore be speculative.

In another "letter to the editor", Coleman, Bell, and Sleet (1983) analyzed the proportional registration ratio (PRR) of the incidence of cancer in 10 electrical occupations in Southeast England for the period 1961 to 1979. The total registration number (cases reported by hospitals) was 113 and was 6 or less in six of the ten categories. The PRR was less than expected in two categories (radio/radar mechanics and professional electrical engineers). The investigators noted the small number of cases used in the analysis, and differences in listing occupation by hospitals (cases) and by government census (controls). They further noted that the literature does not support a conclusion that electromagnetic fields and death by cancer are related.

Coleman, Bell, and Skeet (1983) generally followed the methods used by others but pointed out several limitations of methods employed. They did not conclude clearly that a relationship exists between electromagnetic fields and cancer. The obvious limitations of the study, and inconsistencies between their tabular data and others, suggest that no conclusions should be drawn from the report.

RESIDENTIAL EXPOSURE

Wertheimer and Leeper (1979) suggested a link between the development of cancer in individuals less than 20 years of age and the configuration of electric currents around the homes where these persons lived in Denver, Colorado. The investigators related the records of deaths due to childhood cancer in the greater Denver area, to the presence of electric power lines.

The "cases" consisted of 344 children who died from cancer before the age of 19 during the years 1976 to 1977. The same number of children--not diagnosed as having cancer--were matched to "cases" according to date of birth. The residence of the "cases" and the controls were classified into two groups: (a) HCC--High Current Configuration, and (b) LCC--Low Current Configuration, starting from the distribution of electric cables around the houses. The cancers were classified as leukemias, lymphomas, cancers of the nervous system, and others. The authors noted they had controlled for the following variables: neighborhood, traffic routes, social classes, family composition, age, and sex.

The analysis indicated that more children resided in homes where the configuration of electric cables suggested an elevated exposure (HCC). In addition, the authors mentioned that there is a "dose-response" relation between the onset of cancer and the levels of current. In their discussion, the authors attributed these results to the direct effect of electrical currents and largely to the effect of alternating magnetic fields which accompany the electric current.

This report included over-simplified explanations, questionable assumptions, debatable interpretations of data, and seemingly unjustified conclusions. It is additionally troublesome because the body of the report presents interpretations that were purported to be unequivocal, but were not supported in the authors final discussion.

Wertheimer and Leeper did not relate effects to actual fields in a quantitative manner. They estimated the exposures by looking at wires outside the houses. On this basis they made distinctions between high and low electromagnetic fields, leading to the conclusion that high-exposure homes produced more cancer victims.

In their discussion, the authors go much too far in the interpretation of their results; their commentaries concerning the mechanisms of action are more personal hypothesis than observed facts. The greatest weakness of the report resides, however, in the fact that the exposures weren't codified according to a blind study. The person who estimated the exposure knew the group to which the subject belonged. This weakness became, at the outset, a significant bias.

The over-simplified explanation of the nature of electric power systems, which apparently is believed by the investigators to be justification for not measuring magnetic field intensities, erodes confidence that the views expressed by the investigators are reliable.

Association between leukemia in the young and residential exposure to power lines was investigated by Fulton et al. (1980) in Rhode Island to confirm or invalidate the results of the earlier study conducted by Wertheimer and Leeper (1979). The "cases" consisted of 119 persons up to 20 years of age who developed leukemia between 1964 and 1978. The controls consisted of addresses of 240 persons matched according to birth date.

As in the study by Wertheimer and Leeper (1979) exposure was measured by considering the configuration of electric cables near the homes of the cases and the controls. In their analysis, the authors controlled for age at the onset of the leukemia, and socioeconomic level.

Leukemia in persons up to 20 years of age reported by hospital authorities during the years 1964 to 78 was studied. Addresses at birth, intermediate years, and at time of treatment were obtained. There were 119 patients with a total of 209 addresses. Controls were selected by a stratified random sampling of birth certificates, and two controls were matched to each case by year of birth only (240 total). Only the birth addresses of controls were obtained.

The power lines within 50 yards of each case address were noted by visual inspection, as were those near control addresses at birth. The investigators note that some power lines may be buried, and therefore were not recorded.

Due to urban redevelopment and other reasons, about 5 to 8% of the addresses could not be noted. The investigators argued that using only birth addresses of controls was not a severe limitation because "the Rhode Island population is fairly stable."

Using the Wertheimer and Leeper (1979) criteria for categorizing power lines by visual inspection, the investigators employed a somewhat complicated weighting factor to estimate magnetic field strengths at each address. The weighting factor included a field intensity factor which presumed that intensity diminished as the square of distance. The control addresses were then separated into four distinct quartiles. The case addresses were then assigned to appropriate quartiles according to the weighted exposures, and it was found that the control addresses also fitted the quartiles much like the controls. this quartile-fitting of cases was done for all age groups, redone for several distinct age groups, and for groups categorized by socioeconomic status. With regard to the latter, the investigators stated there is a relationship between family income and leukemia (reference cited).

The investigators concluded no relationship exists between the incidence of cancer in children and power line proximity in Rhode Island. They suggested that the Wertheimer-Leeper finding, if valid, may be small, or may be due to some interacting variable unique to Denver. They further suggested that measuring fields in residences may be important.

As in the Wertheimer and Leeper (1979), study this report has several flaws which diminish the strength of the study. There are insufficient health, medical, and environmental data to permit an unequivocal conclusion. The investigators depended upon electromagnetic categorizations espoused by Wertheimer and Leeper (1979), and these are clearly open to question.

The failure of the investigators to determine intermediate addresses of controls is not supported sufficiently by the statement that the Rhode Island population is relatively stable. They reported that 53 of 119 cases (45%) had at least two addresses, and there is no reason to believe the same would not have been true of the controls.

As in the Wertheimer and Leeper (1979) report, it is not possible to estimate magnetic field intensities produced by power lines without measured data obtained over time. There are too many factors which affect power line currents, and it is unlikely that all those factors could be identified and

reliably defined. There is considerable doubt among most engineers that one-time measurements truly characterize field levels.

Wertheimer and Leeper (1982) conducted another survey of cancer incidence among adults in four locations in Colorado (Boulder, Longmont, suburban Denver, and Central Denver). An attempt was made to relate the incidence of cancer to the presence of presumed high current-carrying power lines. The study was patterned generally along the lines used by the investigators to study cancer in children in Denver, reported in 1979. There were some differences in detail, but the same presumptions about current levels and magnetic field intensities formed the basis of the analysis. Without the benefits of measured data, power lines were categorized qualitatively according to expected current levels. Six categories were used rather than the four used in the previous study.

The "cases" consisted of 1,179 adults who were deceased or developed cancer during the years 1967 to 1975 and 1,179 adults deceased or living who did not have cancer. The authors noted that they controlled for sex, age, year of death, urbanicity, and neighborhood and socioeconomic status. The measurement of exposure was, as previously, based on the configuration of the wires of the distribution lines near the homes of the subjects. In the estimation of exposure, the authors considered the place of residence for the 10 years which preceded the diagnosis of cancer.

The cases consisted of all cancers. According to the authors the adults who developed cancer lived for longer periods in the houses considered to have high electric currents (HCC). They suggested a dose-response relation between the level of current and the incidence of cancer. The cancers for which a significant excess was observed included cancers of the nervous system, the uterus, the breast, and lymphomas. In their discussion, the authors attributed the cause of a marked excess of cancer to the magnetic fields which accompany the alternating current.

This study has numerous weaknesses. The methodology is awkward and nebulous. The weakest point is the fact that the exposure was not coded blind. This weakness alone caused significant bias at the outset. The method allowed many imprecisions; the authors did not tell us that their evidence included people who changed address; the data were not chosen in a uniform manner in the 4 regions; and the proportion of the deceased varied greatly

between the towns and the age group. Such variations ought to be the subject of a separate analysis.

As in the earlier study, the authors go much too far in the interpretation of their results. The engineering basis of the study is inadequate.

The critique for the investigators' study of cancer in children (Wertheimer and Leeper 1979) generally applies. In addition, there are other concerns. The statement is made that currents in single-phase lines are especially low, and therefore magnetic fields produced by such lines also are very low. The statement is not supported and is of questionable validity. Single phase currents can be highly unbalanced, with high resultant fields.

Discussion is presented as to why a causal relationship should be expected between cancer and high current conductors. None of the points raised are supported by data or clinical references. In several cases the discussion contradicts statements made in the 1979 study. For example, a socioeconomic difference is noted, and by means of a series of assumptions, the difference is connected to a presumed length of exposure. The discussion leads the investigators to conclude that the latent period for the cancer is quite long. The opposite conclusion was reached in the 1979 study from a different set of presumptions. This study, as the previous one, should be regarded as speculative and does not provide any useful information about any possible relationship between power systems and cancer.

Tomenius, Hellstrom, and Enander (1982) attempted to show a relationship between transmission line magnetic fields and cancer in Stockholm, Sweden. Visual inspections were made at the listed birth residences and at the addresses listed at the time of diagnosis of cancer. Electrical systems and equipment that were visible and within 150 meters of the residences were noted, but only one of 5 possibilities was recorded, in the following order of priority: (1) 200-kV transmission lines, (2) substations, (3) transformers, (4) electric railways, and (5) subways. Magnetic field intensities were measured at entrances of each residence. Measuring equipment is identified, and calibration method briefly described.

A total of 400 cases was identified as having been born and resided in the same church district of Stockholm County at the time of diagnosis. It was not reported whether addresses changed. The remaining 316 cases moved from their church districts, but remained in the county. Nothing was said of

intermediate addresses. The total number of case addresses was given as 1,162 rather than 1,132 as in the text and only 1,129 in an accompanying table.

Controls were matched to the cases by age, sex, and church district of birth. The total number of control dwellings is given as 1,015 in the text, and 969 in the table. The text notes that some addresses were demolished, and others were vacant.

Only 119 of the 1,129 case addresses had visible electrical systems within 150 meters of the dwelling. Almost one-third (32) were near 200-kV transmission lines, and 36 were near electric railways. Those two categories were also the most prevalent for the controls (45 and 37). Only 77 of the 969 control addresses were near visible electrical systems.

The investigators noted that many buried electrical systems are used in Sweden, but no attempt was made to identify their locations.

The range of measured magnetic field intensities was 1×10^{-3} to 1×10^{-6} G, with an arithmetic mean of 0.69 mG. The investigators state that very low values were expected because most elecrical systems are buried cable, and substantial field cancellation was therefore expected. The highest fields were measured near 200-kV transmission lines (2.2 mG, mean value).

All measured data are listed in a table under columns for the various types of observed electric systems or equipment, arranged in rows of 1 mG increments up to 20 mG. The number of case and control addresses are listed for each field intensity. The investigators conclude that the study neither confirmed the existence of a causal relationship between magnetic fields, nor provided data which would prove that no such relationship exists. The reported study is incomplete in too many respects to be conclusive, or to provide much useful data.

The mean arithmetic values of field intensity between cases and controls were substantially different at case addresses for only three types of systems. They were

System	Case	Controls
200-kV transmission	1.8 mG	3.3 mG
Subway	0.8	0.5
Substations	0.8	0.5

The intensities were very similar for all other systems, and were practically the same for the total number of cases (0.69 mG) and controls (0.68 mG). It may be particularly significant that the number of cases near 200-kV transmission lines were much higher than the number of controls (32 versus 13), but the magnetic field intensities for cases were significantly lower. At substations the numbers were 7 and 5, and at subways the numbers were 14 and 16, respectively for cases and controls.

The data show no consistent trends about the possible relationship between magnetic field intensity and cancer. The measurements strongly suggest that the Wertheimer-Leeper method of categorizing electrical systems is not useful.

Because the Wertheimer and Leeper (1979) report has generated considerable interest and concern the details of the work warrant rigorous review and analysis. Such analysis will serve well not only for this study, but it will provide a basis for examination of other comparable reports.

Field Procedures

In the Wertheimer and Leeper (1979) study the birth and death address of each case was visited (or only the birth, or only the death, if the information was so limited). A map of the immediate vicinity was drawn, and the measured distances between the residence and visible power lines and substations (in a few cases) were noted. The same was done for the controls. Primary distribution lines were classified as "large gauge" or "thin," depending upon whether they were larger than secondary wires. The following were classified as High Current Configurations (HCCs):

(a) large gauge primaries within 40 meters of homes.

(b) a group of 6 or more thin primaries within 40 meters of homes.

(c) a group of 3 to 5 thin primaries within 20 meters of homes.

(d) high tension wires (50 to 230 kV) within 20 meters of homes.

(e) "first-span, 240 Volt secondaries" within 15 meters of homes.

The investigators identified item (e) as secondaries "issuing directly from a distribution transformer that has not yet lost current through a service drop beyond the transformer pole."

All other configurations were classified as Low Current Configurations Cs) and included the following:

(a) second-span secondaries (secondaries separated from a distribution transformer by one or more service drops, excepting service drops directly at distribution transformers).

(b) short first-span secondaries (a first span serving no more than two residences, regardless of distance to residences).

(c) residences beyond the last pole of a secondary.

(d) first-span secondaries more than 15 meters from residences.

The investigators did not mention whether there were primaries more than meters from residences and how they were classified.

Denver has been a high growth area, many new primaries have been installed :ently, and the distinction between new and old primaries is not clear. The llowing information was given in the text:

(a) 71% of the primaries were old, and <u>assumed</u> to exist before 1956 at pre-1956 case addresses.

(b) 49% were old at pre-1956 control addresses.

(c) it was not clear whether new primaries replaced old primaries or represented recent system growth (since 1956).

(d) because of (c) above, all pre-1956 addresses were coded only according to secondary systems.

(e) the technique described in (d) was regarded as unimportant because proximity of primaries was associated most strongly with recent addresses.

(f) for the birth addresses:
- 31% of 272 case addresses were near "unadjusted" primaries.
- 22% of 272 control addresses were near "unadjusted" primaries.

(g) for the death addresses:
- 29% of 328 case addresses were near "unadjusted" primaries.
- 19% control addresses were near "unadjusted" primaries.

The locations of the power systems and measurement points are not ›ntified. The measurement methods are not described, and the important ıracteristics of the power system are not given. The currents conducted in ' of those systems depended upon their electrical design characteristics, ›ir cable geometries, the type of connection to and the nature of system ıds, the impedance characteristics of the entire system network, temporal 1 spatial load variations, interconnections with other electric networks, 1 many other factors. The data have very limited practical application in › absence of adequate information about these factors.

The applicability of findings in this report is questionable especially ıce the investigators' themselves noted that "current flow most probably has :ered since subjects' residency" and the statement that "it was rarely ısible to measure fields." Current flow was nevertheless presumed <u>not to</u> <u>'e changed</u> over the years in categorizing about 25% of the cases studied. le it is recognized that measuring field intensities in residences is an ›osition on occupants, and are time-consuming they are imperative if a study this nature is to be of value.

The investigators classify power systems solely on the basis of limited 'sical characteristics and spatial distribution of residences. The ıssifications are therefore <u>qualitative</u>, and have extremely limited :fulness. As noted earlier, the basis for classification is practically ıningless and unconventional. The information is not useful for a 'initive study.

The unconventional and incomplete basis for classifying power systems is ıppropriate to the nature of the study, provides no engineering basis for :a analysis and interpretation, and is therefore misleading. Assumptions le in classifying addresses are important and unsupported. They may ›resent significant sources of error, but this cannot be determined from the ıited information given in the report. Primary circuits were ignored at ›-1956 case and control addresses because it was not clear when primary 'cuits were installed. Classification was made on the basis of secondary 'cuits only, but the number of addresses is not given. The investigators ıore the fact that secondary circuits also would likely have changed when maries changed, and therefore classification by secondaries could be as 'oneous as classification by primaries. Since secondary circuits could be

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uirements, and should note potential biases in selection of subjects, in surements, and in follow-up that may affect the inferences being derived arding the effects of the fields. The sample must also be large enough to e it possible to detect an increased risk.

An outstanding problem of epidemiological studies of powerline exposure is ated to exposure assessment. Typical of the situations which exist in the erature are studies which provide no documentation of dosimetry. Often y broad categorizations such as "exposed" or "nonexposed" are provided. t of the reports on humans demonstrate a lack of adherence to rigorous dy design, analyses, and discussion. Control groups are frequently king. Population selection criteria and methods are usually not cribed. Control of confounding variables, such as age, occupation, health tus and habits, economic status, etc., is often not considered. Applied tistical methods may not be described or, largely because of study design, not measure the strength of association vis a vis relative risk or odds io.

There is considerable difficulty in establishing the presence of, and ntifying the frequency or severity of, "subjective" complaints. lividuals suffering from a variety of chronic diseases or acute ailments may ibit the same dysfunctions as those reported to be a result of exposure to ctric or magnetic fields. Psychosocial interactions can also influence siological reactions. Thus, it is extremely important to rule out other tors in attempting to relate electric or magnetic field exposure to nical conditions.

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It has been suggested these reports establish a causal link between exposure and leukemia. This is by no means valid. To affirm the existence of a causal link, there is a need for studies much more sophisticated and of a far greater scope. It has also been suggested the reported association between leukemia and cancer and exposure to electric or magnetic fields is perhaps confounded by factors other than the fields per se.

Wright, Peters, and Mack (1982) have noted "The precise cause of the excess of leukemia we have observed is not clear. The occupation grouped as sharing exposure to electric and magnetic fields undoubtedly share other exposure. While significant exposure to ionzing radiation is probably not present in most of these jobs, metal fumes, solvents (including benzene), fluxes, chlorinated biphenyls, synthetic waxes, epoxy resins and chlorinated naphthalenes are other exposures that may be shared."

In further studies it will be necessary to consider very closely these other occupational exposures if one wants to clarify the link between leukemia and exposure to electric and/or magnetic fields.

Reports of effects of electric and/or magnetic fields among humans must be put in perspective. Careful analysis of these reports does not provide convincing evidence of clinical or other health problems among individuals or populations working or residing in proximity to the electric and magnetic fields from power lines or industrial sources. There are numerous problems in designing epidemiologic or incidence studies. It is essential that the multiple environmental factors which may interact among themselves and with personal characteristics of an individual be evaluated. There is always the danger that real factors may be overlooked, leading to a false association with factors of initial interest. The validity of application of the epidemiologic method to the study of the health impact of a factor such as a transmission line or substation environment is largely determined by the ascertainability and definition of an effect as well as the intensity of the exposure.

One problem is to select paired populations that are not systematically loaded with some other bias. The control or comparison group should be comparable with the case group, i.e., the exposed group, in all relevant characteristics except for the exposure itself. The report of the study should provide the data needed to assess whether the study has met these

individuals from one class of occupation to another. This selection leads to the problem of interpreting final jobs, since associations with the final job may lead to false conclusions if the job was entered relatively late in life.

In determining proportional mortality rate the number of deaths ascribed to a particular disease is expressed as a proportion of all deaths within a specified population. Similarly, in clinical studies the incidence of a disease is sometimes reported as the number of patients with that disease as a proportion of all patients seen at the same institution.

Such proportional rates do not, of course, express the risk of members of the population contracting or dying from the disease. Comparison of such rates between areas or between population subgroups may suggest that a difference exists that is worth investigating. But until rates can be computed against a population base, it will not be known whether the difference relates to differences in the sizes of the numerators or the denominators of the compared rates (MacMahon and Pugh 1970).

The major flaw of the proportionate morality ratio is that it says nothing about total force of mortality for a given occupation (Milham 1983). All occupations have a total PMR of 100. Also, since the cause-of-death specific PMRs must sum to 100, a very high or low PMR in a common cause-of-death group will affect the other PMRs for that occupation. The method has had numerous critics.

Within each age group the proportion of deaths for all causes sum to 1 (i.e., 100%). A large excess or deficit from one cause of death or several causes will decrease or increase the proportions dying from other causes. Thus, the PMR indicates only the importance of a specific cause of death relative to other causes in the same occupation, and does not measure the risk of death or the overall mortality (Petersen and Milham 1980). Further discussion of mortality/incidence ratios will be found in a recent paper by Lanes and Poole (1984).

CONCLUSION

There is no doubt that the works examined so far are not very probing. The numbers are small, the epidemiological methodologies are often weak, and the statistical analyses utilized are not solid. The possibility of a link between leukemia and cancer and exposure to electrical and magnetic fields has been raised and only responsible research can refute or confirm these reports.

surveillance studies. Any attempt to rigorously test hypotheses generated from these data must be carefully controlled for confounding.

Alternatively, at least two possible biases exist that could lead to an artifactual association of cancer types with certain populations. The accuracy of cause-of-death certification for specific forms of cancer on death certificates may range from 60 to 90% on the average (Engel et al. 1980; Gittelsohn and Senning 1979; Percy, Stanek, and Gloeckler 1981).

The second possible bias that could lead to an artifactual association of cancer types with selected populations would occur if the death or incidence rate of one or more common diseases in the occupation of interest were lower than average. In proportionate analyses, this would result in an artifactual increase in the proportion of the other diseases.

Most surveillance studies have not been able to control for confounding, and there are many possible biases. Dubrow and Wegman (1983) have identified the 178 strongest and most consistent occupation-cancer associations from 12 major surveillance studies. These include lymphatic leukemia among farm owners, and leukemia among lawyers, judges, mechanics and repairmen. They also found the strongest and most consistent brain and nervous system cancers among students, bank officers, lawyers and judges, teachers, engineers, accountants and auditors. In regard to the report by Milham (1982) it should be noted that he (Milham 1971) in a study of leukemia death certificates in Washington state and Oregon was able to confirm and extend a previously reported (Fasal, Jackson, and Klauber 1968) association of leukemia with farming occupations thus his association of leukemia with electrical workers is not unique.

Occupational mortality studies suggest that observed differences in the mortality pattern within or between occupations primarily reflects variations in specific exposures within or between occupations and only secondarily reflects behavior patterns associated with individuals. This assumption does not actually hold true, since it is known that certain types of individuals select their vocation, or are prescreened by physical examinations as a condition of entry (Petersen and Milham 1980). Disease experiences of persons in the years prior to choosing a vocation play a major role among preselection factors. Similarly, the disease experiences and psychological factors associated with a primary job may aid in determining transfers of certain

Associational studies such as those done without specific hypotheses are relatively crude and do not take into account important potential confounding variables. As such, they cannot be used to prove a causal association between a population and a type of cancer (Dubrow and Wegman 1983).

Many of the associations seen in any one surveillance study will be chance associations. Any time many statistical comparisons are made, a certain number will achieve statistical significance by chance alone (Dubrow and Wegman 1983).

The strengths and limitations complement each other to some extent. For example, the quality of occupation and cause of death information obtained from death certificates is known to be mediocre (Anderson 1972; Buechley et al. 1956; Engel et al. 1980; Gittelsohn and Senning 1979; Milham 1976; Percy, Stanek, and Gloeckler 1981; Wegman and Peters 1978; Wigle et al. 1980).

Investigators inevitably express their own biases and prior knowledge. While results may point to an occupational or residential cancer problem, seeing it as a problem may be influenced by previous reports.

Numerous factors need to be taken into account in proposing an hypothesis that an occupational cancer problem exists in a given population. These factors include the following:

(1) The magnitude, level of significance, and consistency of the association of the population with a type or types of cancer.

(2) The number of cancer sites with which the population is associated, as well as the relationship among those sites. For example, if several sites in the respiratory and upper alimentary tracts are elevated, this could suggest the possibility of an inhaled carcinogen.

(3) The possibility of confounding factors or biases explaining the association(s).

(4) The likelihood of occupational exposure to known or suspected carcinogenic agents.

As already noted, most surveillance studies are relatively crude and do not take into account potential confounding variables such as cigarette smoking. It is important to consider the possibility of confounding factors explaining cancer associations with selected populations identified from

installed or "beefed up" after the case's birth, or the currents in the primaries were increased after birth.

The number of male cases was 57% of the total and appears consistent with the belief that cancer is more prevalent in males than in females. Whether the percentage is higher than should be expected is not discussed. An analysis based on total regional child population would appear to be more appropriate.

The analysis of sex differences is especially tenuous. The references used to categorize the data are inappropriate. The cited work refers to direct current (static) electromagnetic fields and fields of much higher intensity than produced by power lines. No information or any other justification are presented for the conjecture, suppositions and speculations about aborted male fetuses and exposure initiated post-natally. The scenario presented by the investigators simply cannot be taken seriously. The analysis of sex factors is based on inappropriate reference material, unsupported suppositions, and unjustified speculations, and is not credible.

CRITIQUE OF EPIDEMIOLOGIC ASSOCIATION STUDIES

In any review of human surveys concerned with possible extremely-low-frequency (ELF) field effects, one has to be aware of the critical importance of how epidemiologic studies are designed and executed and how results are interpreted. Reports of clinical effects of electric and/or magnetic fields among human populations present serious difficulties which stem from the many publications in which pertinent material is not presented, and the data are variable or internally inconsistent. One has to beware of "spurious correlations." Correlations in themselves do not necessarily establish cause-effect relationships. An outstanding problem of epidemiological studies is related to exposure assessment. Often only broad categorizations such as "exposed" or "nonexposed" are provided. Most of the reports on humans demonstrate a lack of adherence to rigorous study design, analyses, and discussion. Control groups are frequently lacking. Population selection criteria and methods are often not described. Control of confounding variables, such as age, occupation, health status and habits, economic status, etc., is often not considered. Applied statistical methods may not be described or, largely because of study design, do not measure the strength of association via relative risk or odds ratio.

Young Cases Versus Older Cases

The investigators note that Table 6, which separates the data according to groups 0 to 6 years of age and 6 to 19 years of age, disproves the theory that the HCC effect on cancer may not be evident early, but may instead be a delayed effect.

Despite the unsupported assumptions which limit the usefulness of the report, and the unorthodox description and classification of power systems, and the previous statement by the investigators that categorizing the data according to types of cancer may not show a causal relationship between presumed HCCs and cancer, the statement is made that age categorization disproves the theory of a long latency period for cancer. The presumptions concerning birth addresses and lack of intermediate addresses are especially troublesome in this regard, and the statement is not supported by the questionable data.

Sex differences

The investigators stated that there is a prevalence of cancer among males in contrast to females (no age information or reference provided). Males comprised 57% of the cases, and 49% of the controls. There was an excess of HCC for both males and females over controls, with the trend stronger for males: 51% HCC for male cases at birth, death or both addresses and 45% for females; and 28% HCC for male controls at birth, death or both addresses, and the same for female controls. A significant male case excess also was noted when the birth address was LCC and the death address was HCC, and when cancer developed after 9 years of age at a primary HCC address. The investigators stated that significant male case excess occurred only for two conditions: when birth addresses had a lower current configuration than the death address, and when cancer developed one year or more post-natally at a stable address near primary wires.

The investigators stated that cited literature demonstrates there is a post-natal effect, and their data characterization is evidence of such an effect. The following explanation was given: male fetuses at HCC addresses may frequently abort, and male fetuses at LCC addresses which reside post-natally at HCC addresses may then develop cancer. A second argument also was given: it is always possible that primary wires near case houses were

relationship may not be a causal one, alternative explanations being artifactual or an unknown effect on the body's ability to resist cancer.

Socioeconomic class

A reference is cited as a source of the statement that cancer is more prevalent in higher socioeconomic groups. The investigators felt that the trend in their data is insignificant. Socioeconomic class as listed in their Table 8, was based on the father's occupation at the time of the case or control's birth, and was determined according to classes given in a referenced document.

The investigators noted that bias is unlikely in the controls even though lower class controls were discarded if addresses were not traceable. Justification for the statement is that discarded controls were equally from the lower and upper classes. Without identifying Class III Controls, they noted that Class III Controls were disproportionately retained.

Identifying social class by occupation of the father at the time of the birth of the child may be inappropriate. Doing so presumes no upward mobility. It is not apparent that the cited reference supports this method of defining social class. The investigators apparently do not question the fact that their data seem too inconsistent with the conclusions of the reference, and may be inconsistent due solely to study methodology.

The analysis and its interpretation is further confounded by a discussion of Class III Controls, not previously mentioned or defined in the report.

It is not apparent that the data in Table 8 represent any useful information about socioeconomic class because important information is lacking. What is the proportion of the upper class cases with respect to the total upper class population of children in Denver? Is the proportion higher or lower than might be expected from the cited reference? Likewise, what are the proportions for the middle and lower classes with respect to expectation? If any of these proportions are higher than expected, can the higher expectancy possibly be attributed to an excess of HCC birth addresses? Conversely, can lower proportions than expected be attributed to a low number of LCC birth addresses? It would seem that an analysis of this kind would be more convincing.

Table 9 according to the investigators. Heavy traffic is defined as a daily traffic count of 5,000 vehicles or more, and is based on highway department maps. The investigators comment that the HCC-case excess was apparent in all neighborhoods, and a significant excess occurred only when the nearby traffic and HCCs coincided, not just when heavy traffic was evident.

Substation Proximity

The investigators noted that none of the 702 control addresses (including those not included in the study) were within 150 meters of a substation, but 6 of 491 case addresses (1.5%) were within 150 meters of a substation and within 40 meters of a large primary. They suggest only 1 in 1,000 homes in Denver are within 150 meters of a substation. They also noted that each of the 6 cases resided at that address no more than three years prior to illness. Since only 6 of 272 cases resided relatively close to substations, the information does not appear to be particularly significant.

Bias

The investigators regarded their study as exploratory, and therefore did not classify addresses "blind". They suggest there was no bias, as demonstrated by a check with an assistant. The assistant classified 70 cases and 70 control addresses blind, and agreed with the investigators' classification in 91% of the instances and in 5 of 12 disagreements upgraded the classification to HCC. It is not stated if the agreement was more pronounced for cases or for controls, and which were upgraded. Another blind study was conducted in Colorado Springs and Pueblo. In that study 32% of 65 cases were HCC, and only 18% of the controls were HCC. The correlation was strongest for cases before age 6, possibly because others had moved many years before cancer onset.

Type of cancer

The authors' Table 5 lists data according to four types of cancer for birth addresses and for death addresses. The cases near HCCs exceeded the controls near HCCs in every category for both birth and death addresses. Both cases and controls at LCCs were greater than at HCCs in both address categories. The investigators suggested the data may show that the HCC-cancer

regardless of neighborhood. The neighborhoods are insufficiently identified and described in terms of a wide range of possible ambient environmental conditions for the authors' Table 6 to be meaningful. The apparent failure to match cases and controls by general neighborhood dilutes the credibility of the data and their interpretations, even if a neighborhood match had been made.

Environmental characterization of neighborhoods is important, and especially so for urban and suburban neighborhoods. Many types of pollutants have been identified in air, water, and soil in urban-suburban areas, and at least some are either known or suspected carcinogenic agents. None of the common pollutants or those that might be unique to particular neighborhoods are addressed by the investigators with one exception (heavy traffic). The presence of certain types of industries could be a contributing factor as, for example, the production of compounds which produce hazardous waste as a by-product.

Use of Suburban Controls

The investigators noted that there was an excess of suburban controls used in the study, but this was insignificant to the analysis. No numbers are given. The number or proportion of suburban controls used in the study is not identified, but is said to be insignificant. It is unclear whether any cases were located in the suburbs. Evidently at least some suburbs were classified as such from a municipal planning document for the period 1960 to 1970, and was therefore considerably outdated when the study was conducted. Moreover, planning documents do not always resemble actual conditions, as many plans never come to fruition or are substantially changed after original plans are adopted and documented. Important environmental conditions can differ between city and suburbs; they should be identified and reported in a study of this type. Ambient environmental conditions which characterize neighborhoods, and which may identify significant differences between neighborhoods of cases and controls, and which can be important in health studies, are not reported or discussed, thereby limiting the credibility of data interpretations.

Traffic Routes

A reference is cited which supposedly relates cancer to heavy traffic routes. A "mild" excess of cancers on heavy traffic routes is suggested by

File II. The addresses of controls were handled the same way as the addresses of cases; that is, a control matched to a birth-residence case was presumed to have only a birth residence history, and so on.

It appears that possible intermediate addresses of cases between birth and death were not determined or traced. There is no reason to believe that intermediate addresses were not possible for at least some cases. The same holds true for controls. A complete residence history is essential, and if obtained, should be reported. In the absence of this information, the report is limited and not definitive.

No justification is provided for assuming the same birth and death addresses for cases when one or the other was not available. Since 26% of the cases were not traceable with regard to both addresses, and the time of residency is neither stated nor considered, the data are unreliable to a significant degree.

The description of selecting controls is incomplete. It appears that File I Controls were matched to cases only on the basis of age. It would seem possible that reasonably good matches could be made on the basis of age and general residential vicinity in a metropolitan area as large as Denver. Doing so would enhance the quality of data. Moreover, it should be clearly stated if the birth listing were chronological or alphabetical. Since some illnesses are known to be racially selective, it may also be important to identify racial characteristics, state whether there is any known cancer relationship with race, or whether such a relationship is unknown or uncertain. Similarly, were matches made to account for sexual similarity? Why were siblings purposely not used as controls?

The selection of File II Controls also is incomplete. How many attempts were made to identify and trace a File I Control before a File II Control was matched to a case? It would seem that the daily birth rate in Denver would be fairly high, suggesting a fairly high success rate in tracing and matching File I Controls. The absence of information is of concern. How many File I Controls were used? How many File II Controls were used, and how distant from Denver did they reside, and for how long?

Type of Neighborhood

The investigators suggested that cases at HCCs outnumber controls at HCCs

systems are sources of concern about residence coding and reduce confidence in data classifications, interpretations, and findings relative to proximity to HCCs and LCCs.

The investigators noted that more cases than controls lived near presumed HCCs for stable addresses and moved residence (the importance of intermediate addresses was noted earlier). The total numbers of cases and of controls are different and unexplained. It is not clear whether a particular address was listed more than once if it was in proximity to more than one type of wire configuration, but that seems to be the case. If so, the authors' table of measured magnetic field data (Table 1) could be especially misleading. The magnetic field intensity at an address could be produced by multiple sources and be much higher than inferred from Table 1. Furthermore, the field intensity at a presumed LCC address conceivably could be higher than at a presumed HCC address under some circumstances.

Data Selection

Death certificates were obtained for persons up to the age of 19 in the Denver area (not defined) who died of cancer and had addresses in the area between the years 1946 to 1973. Birth addresses were obtained from birth certificates, and death addresses were those listed in city directories for the two years prior to the diagnosis of cancer. If no birth address could be found, only the death address was used; if no death address could be found, only the birth address was used. A total of 344 cases was studied. Of these, 72 birth addresses (21%) could not be found; death addresses could not be found for 16 (5%). Assumptions therefore had to be made for 26% of the addresses. The investigators do not mention intermediate addresses, or time of residency at any address.

Controls were selected from the next listed birth in the Denver area birth certificate listing. These were identified as File I Controls. Siblings were skipped. Presumably the listing was chronological. A File I Control was matched to an appropriate case if the control's addresses (birth and at time of case's death, presumably) could be traced in Denver. Otherwise a File II Control was selected from an alphabetical listing of all Colorado births for wide spans of years: 1938 to 1958, 1959 to 1969, and 1970 to 1974. It is unclear how many traces of File I Controls were attempted before reverting to

called HCC or LCC by the investigators, the basis for classification remains questionable. The argument that proximity to primaries was most strongly associated with cancer at recent addresses (presented by the investigators) is suspect in the absence of the number of "old" primaries that was ignored and their relative importance between case and control addresses vis-a-vis HCC and LCC classifications. The information provided to support the argument appears easy to misinterpret, but it seems that the number of ignored primaries was substantial. Ignoring the possibility of changed secondaries, and the substantial primary numbers, suggests that significant coding errors could have been made by the investigators. The suggestion is further reinforced by the admission that it was not determined when newer primaries were installed, and whether the newer primaries were truly new installations or replacements of older wiring. Finally, the investigators ignore their earlier comment that current magnitudes do indeed change over a period of years. The importance of ignoring this possibility is not mentioned.

No mention is made of recently-constructed dwellings in established neighborhoods. Individual distribution transformers are not necessarily used when new homes are built. It is possible that older transformers are replaced by newer, larger capacity transformers capable of serving a number of consumers. Thus the classification of secondaries can change from LCC to HCC (and vice versa), and this possibility, and its consequences to coding, cannot be ignored without justification.

The investigators also made no mention of buried power lines. Buried lines (either primaries or secondaries) could confound the residence coding if they are used by the public utility and were ignored.

While it may have seemed unimportant to the investigators because of their unorthodox way of classifying power lines, nothing is mentioned about transmission or distribution circuits that may be in the general vicinity but are not directly associated with the residences studied. All lines are not the same capacity, and a high capacity line somewhat further from a residence served by a relatively low capacity line can contribute significantly to magnetic field intensity at the residence. The existence or absence of such lines should have been reported. The inadequate basis for coding residences, the inconsistent method of coding with resulting potentially significant errors, and the absence of information on buried and/or nearby unrelated

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ECOLOGICAL EFFECTS OF EXTREMELY LOW FREQUENCY ELECTRIC AND MAGNETIC FIELDS

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INTRODUCTION

This paper deals with current knowledge concerning the relationship between Extremely Low Frequency (ELF) fields and natural ecosystems. Unless otherwise noted, ELF fields refer to both the electric and magnetic field components at frequencies below 100 Hz. Changes in natural systems in response to disturbance are most often investigated in terms of changes in patterns at some level of organization within the ecosystem. In ecology, the term "level of organization" refers primarily to the organism, population, community, or ecosystem. "Organism" is a term well known to most people and simply refers to individuals for some particular species. "Population" refers to a group of organisms for a particular species that are present at a specific location. An ecological "community," then, includes all populations present at a particular area. The community, combined with the nonliving (abiotic) portion of the environment, forms the ecological system or "ecosystem."

The concept of organization levels provides the basis for the organization of our paper. First, we discuss the levels of organization and the particular parameters associated with each level that might provide a measure of the response to disturbance by ELF fields. Then, we describe the ELF electrical exposure systems present in the environment and current knowledge of the relationships between ELF fields and ecological effects. A summary and recommendations for further study comprise the final section.

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THE ECOLOGICAL SYSTEM: LEVELS OF ORGANIZATION

An accurate judgement of the ecological consequences associated with ELF fields in the environment requires examination of biotic assemblages of one sort or another. This type of examination is usually referred to as "ecological effects detection" or "ecological monitoring" (Gray 1980). Simply stated, ecological effects detection involves "the purposeful and repeated examination of the state or condition of specifically-defined biotic groups in relation to external stress" (Hinds 1984). Ecosystems are highly complex and provide a variety of opportunities for measuring a potential response to electric or magnetic fields. Each level of organizational complexity within the ecosystem has certain strengths and weaknesses for detecting effects associated with ELF fields. Here, we consider some of the ecological characteristics available for study at each organizational level.

The Individual Organism and Indicator Species

Individual organisms have had various uses in environmental monitoring programs. One use for the organism is as a surrogate "filter" to be analyzed as an indicator of environmental quality. Analysis of honeybee tissues or hive products for toxic pollutants is an example of this type of environmental monitoring at the individual level. Another type uses individual organisms as biomonitors. The old practice whereby coal miners took a canary into the mine with them is an example of the use of an animal as a biomonitor. The canary, more sensitive to dangerous gases than man, provided an early warning system for air quality.

Neither the surrogate filter approach nor the early warning system approach appears applicable for the ELF situation. There are currently no known cumulative affects associated with exposure to ELF fields; consequently, there has been little incentive to search for appropriate biomonitoring units. Likewise, there has been no evidence that exposures to fields at levels available in the environment are hazardous to human health, so there has been little impetus for identification of a "coal miner's canary" sensitive to ELF electric fields.

The Population Concept

The "population," in an ecological sense, is a group of individual

organisms occupying a particular place (Smith 1977). The population is also a self-regulating system that helps to maintain stability of the ecosystem. Numerous characteristics of the population are distinct from those of the individual. They include population size (density), natality (birth rate), mortality (death rate), immigration and emigration patterns, demography, growth forms, age and sex distribution patterns, dispersion patterns, and niche size.

Stress appears to play an important role in population dynamics (Chitty 1952; Christian 1963). Stress often results in endocrine imbalances in vertebrates, a potential feedback mechanism from the population to the individual inhabitants. It is not known whether ELF fields influence populations or whether such fields might function in some synergistic fashion with natural stressors such as lack of food, weather, and overcrowding that occur naturally in the environment.

The Community Concept

The ecological community is comprised of all populations occupying a given area and is only limited by a requirement of similar species composition. The study of community ecology is therefore a study of the interactions of populations. Communities are dynamic in that they are in a more or less continual process of change, especially in terms of species composition and productivity.

The replacement of one community by another is termed "succession" and represents an orderly process of community change that culminates in a climax community. Most of the communities inhabiting powerline rights-of-way are successional as a result of disturbances associated with construction and maintenance of the transmission facilities. Studies designed to assess the effects of the associated ELF fields need to account for the fact that the communities themselves are undergoing change. In addition, most transmission line rights-of-way are maintained through the use of herbicides or the selective removal of trees and brush. These maintenance activities tend to hold the right-of-way community in a preclimax condition.

There are special parameters for evaluating the condition of communities, just as there are specific parameters associated with populations. Community level parameters include the following: relative abundance (dominance),

physiognomy (growth form and structure), trophic structure, diversity, and successional stage.

The Ecosystem Concept

Ecosystems encompass the biotic community and the abiotic component. They are characterized as self-sustaining units except for the input of energy. Just as communities are comprised of populations, so ecosystems are comprised of all lower levels of organization.

Most research at the ecosystem level has concerned structural and dynamic attributes. Structural attributes concern the organization of an ecosystem, but they do not address its dynamics. Examples of structural attributes are components (e.g., size of producer, consumer, decomposer, and abiotic components), organization (taxonomic composition, trophic relationships, physiographic/spatial/temporal distribution patterns), diversity (the kinds of species, resources, or utilization of resources in the ecosystem), and connectivity (interconnections of energy, nutrients, and water between ecosystem components or trophic or taxonomic groups). Structural studies do permit comparisons between different ecological systems and in fact are the basis for most impact assessment studies.

Dynamic ecosystem attributes are of particular interest since they address questions concerning the movement of materials and energy, the control of productivity, and response to perturbations. The dynamic attributes include those relating to ecosystem transport, stability, and sensitivity. Transport attributes are concerned with the flow of energy and the circulation of materials. Transport builds on the structural attribute of connectivity. Rates of transport are the focus of the transport attribute. Components of the stability attribute are diversity, successional processes, resistance to disturbance (resistivity), and the ability to recover from disturbance (resilience). Ecosystem sensitivity refers to identification of threshold levels or limiting factors regulating ecological responses. Little is known about ecosystem sensitivity, primarily because sensitivity analyses require extensive data sets for all contributing factors. Analysis, then, usually takes the form of multi-factorial analysis to determine controlling factors or model construction and manipulation. Much current ecological research is focused on identifying the response of particular types of ecosystems to

disturbance and to documenting the recovery process. In this respect, ELF fields are no different than other potential perturbations.

ELECTRICAL EXPOSURE SYSTEMS (ELF) IN THE ENVIRONMENT

Artificial ELF electric and magnetic fields have been present in ecological systems since the first AC power lines were introduced in the late 1800s. Today most of the manmade 60-Hz fields present in the environment are related to the generation, transmission, and utilization of electrical energy. More recently, the Department of the Navy has been interested in developing the use of extremely low frequency signals for communications purposes. This section describes these major exposure systems associated with ELF fields in the environment.

AC Power Transmission Systems

Expansion of the early-day power transmission systems was rapid. Today, with over 485,000 km of transmission lines (110 kV and above), and thousands more kilometers of distribution lines in the United States, power lines are an ubiquitous feature of the landscape.

In addition to the extensive growth in the number of lines built, transmission voltage has consistently increased through the years. Lines operating at 110 kV were introduced about 75 years ago. EHV (extra-high-voltage) lines, 345 kV and above, arrived in the early 1950s. The first 500 kV line was energized in 1965, followed by 765 kV in 1969. UHV transmission lines (1000 kV and above) have been tested since 1967, but commercial UHV lines are not expected to be built in the U.S. until approximately the year 2000.

As transmission voltage was raised, the strength of electric fields produced by such lines also increased. Likewise, magnetic field strength increased as load (i.e., current) levels grew. The technical properties of three-phase, AC transmission line fields have been described in several sources (e.g., Deno and Zaffanella 1982). The discussion in this paper is limited to such general properties and levels of powerline fields as are needed to accompany a discussion of their interactions with ecological systems.

In North America, the electric power frequency is 60 Hz, although harmonics are also present in varying degrees. Electric field strength is

expressed in units of kilovolts per meter (kV/m). Table 1 gives typical maximum vertical electric field strength associated with different transmission line voltages. Figure 1 shows how the strength of the electric field at 1 meter above ground decreases rapidly with increasing distance from the line.

TABLE 1.
TYPICAL AC TRANSMISSION MAXIMUM CALCULATED
ELECTRIC FIELD STRENGTH (Lee 1984)

	FIELD STRENGTH[a]	
Nominal Line Voltage	On Right-of-Way	Right-of-Way Edge
230 kV	2-3 kV/m	0.5-2 kV/m
345 kV	3-5 kV/m	1-2 kV/m
500 kV	7-9 kV/m	2-3 kV/m
765 kV	10-12 kV/m	3-4 kV/m[b]
1100 kV[c]	9 kV/m	5 kV/m

(a) This table is meant to give approximate relative comparisons of maximum electric field strength associated with various classes of transmission lines. Actual field strength is highly variable and depends on line design, right-of-way width, terrain, and operating conditions.

(b) This is the approximate edge of the right-of-way field strength for 765-kV lines operating in six states. An exception is the State of New York, which has an edge of right-of-way "standard" of 1.6 kV/m.

(c) There are no commercial 1100-kV lines in operation, with the possible exception of the USSR. Field strengths in this table are design-criteria for a possible Bonneville Power Administration 1100-kV line.

As noted in Table 1 and Figure 1, electric field strength is highly dependent upon several factors, including the voltage and design of a particular line. It should also be pointed out that electric fields are greatly attenuated by objects such as buildings and vegetation.

The magnetic field strength from transmission lines is generally less than 0.5 mT. Figure 2 is an example of how magnetic field strength also decreases rapidly with distance from the line. Unlike electric fields, however, magnetic fields are not attenuated by most objects, including vegetation or animals.

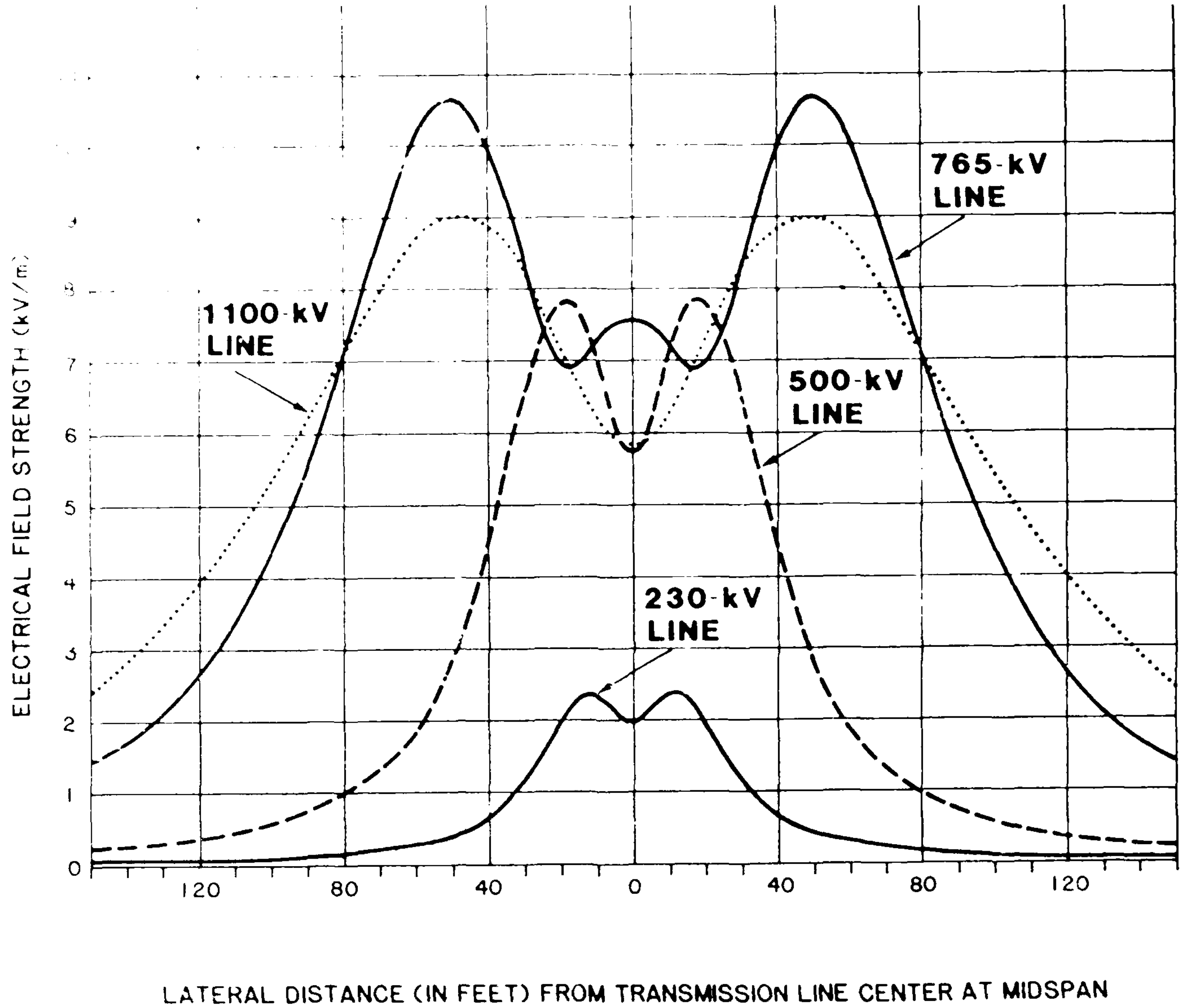

Figure 1. (Electric Field) Calculated 60-Hz Vertical Electric Field Strength at 1 Meter Above Ground at Lateral Distances from Four Selected Transmission Lines. (Actual field strength is greatly influenced by line configuration, operation conditions, and terrain (Lee 1984)).

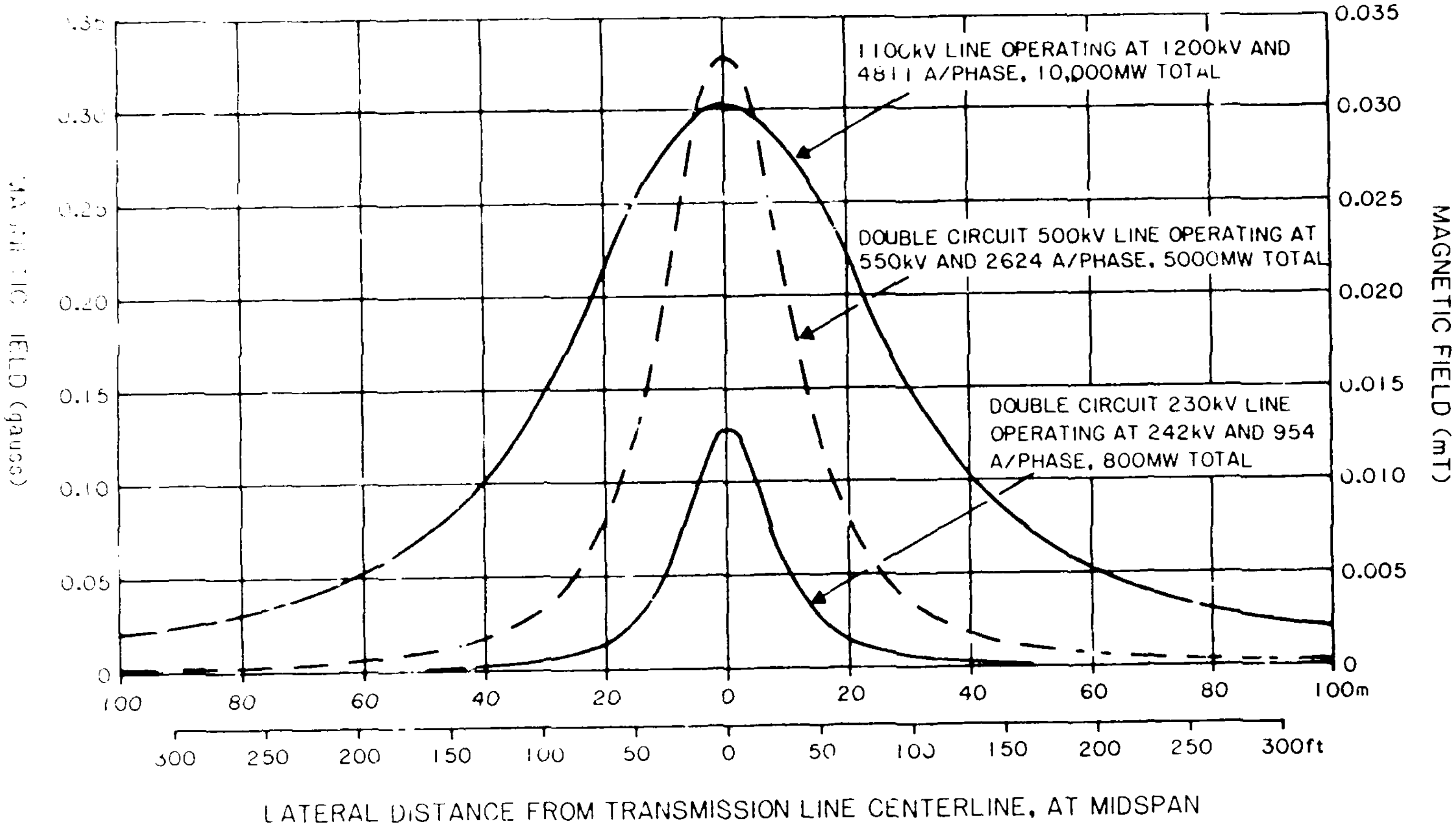

Figure 2. (Magnetic Field) Profile of Calculated 60-Hz Vertical Magnetic Field Strength at 1 Meter Above Ground for 230-kV and 500-kV Double-Circuit Lines, and a Possible Design for a 1100-kV Line (BSTT 1982).

For EHV and UHV transmission lines, it is important to acknowledge the resence of corona in addition to electric and magnetic fields. The presence f corona causes audible and radio frequency noise and production of small mounts of ozone. The occurrence of corona is one significant difference etween the electrical environment of EHV/UHV lines and that of lower-voltage owerlines and the Navy Communication System, where corona is absent.

Corona is primarily a foul-weather phenomenon. During rain, audible noise n the right-of-way of an EHV line may be on the order of 53 to 65 dB(A) epending on line design and altitude (BSTT 1982; Comber, Nigbor, and affanella 1982). Audible noise decreases at a rate of 3 to 4 dB as distance rom the transmission line doubles. During fair weather, some corona occurs ue to irregularities on the surface of conductors (e.g., nicks, insects, ust). Although during fair weather, corona noise may not be measurable above mbient noise, it is still detectable by humans (and presumably animals) ecause of its unique frequency composition. Ozone production from ransmission lines was an environmental issue in the early 1970s. Although zone is produced by corona, a number of studies have indicated that the mounts produced are generally too small to be detected above ambient levels (Scott-Walton et al. 1979).

The Navy's Communication System

The United States Navy has plans to operate two synchronous ELF ommunications stations, one in Wisconsin, the other in Michigan. The purpose f these systems is to deliver messages from the Continental United States to ubmerged submarines operating throughout the world.

The Wisconsin system has one north-south antenna and one east-west ntenna. The Michigan system will have one north-south and two east-west ntennas. The antennas are comprised of long overhead wires, grounded at each nd. Each antenna is driven by one power amplifier. The antennas at the isconsin site will have a total length of 45 km. The antennas at the ichigan site will have a total length of 90 km. The power amplifier output urrent has a nominal amplitude of 300 A and 150 A, respectively, for the isconsin and Michigan sites. The central operational frequency would be bout 76 Hz (Zapotosky and Abromavage 1983).

Power for ELF transmissions is fed to the centers of the antennas. These

ırrents enter the ground at the ends of the antennas through large, ›w-impedance ground terminals. Thus, the electrical path for each antenna is ·om the source, down one-half of the antenna, into the ground and through the ·ound to the other end of the antenna, and back to the source.

Each overhead antenna is to be operated at a voltage relative to the ·ound. Air electric fields will therefore exist between the antennas and ·ound, with a typical ground level field strength of about 150 volts per :ter (V/m) (Zapotosky and Abromavage 1983). Near the ground, air fields will : essentially vertical because the complex conductivity of the ground is so ıch larger than that of air (EPRI 1975). Electric fields are also present in ıe ground, associated with the currents traveling between the two ends of ıch antenna. Near the surface of the earth, these fields will be horizontal, th typical magnitudes of about 1.5 V/m near the ground terminals and 0.14 ıd .07 V/m under the antennas of the Wisconsin and Michigan systems, :spectively.

The antenna and ground currents also produce magnetic fields. Because the ·ound current is diffuse, maximum magnetic field strengths would be found :ar the overhead conductors. ELF magnetic fields are not significantly fected by the earth because the electric and magnetic skin depth (Smythe ›68) is relatively large. For example, the most conductive soils are wet, ·ganic soils with specific conductivities of about 0.1 Siemen per meter (IEEE ›72; Rudenberg 1945) and calculated skin depths at 76 Hz are about 180 ·ters. Values for magnetic field strengths under the antenna near the ·ound's surface are expected to be about 0.06 and 0.03 G for the Wisconsin ıd Michigan sites, respectively. The antenna corridors do not run in a .raight line but are irregular.

The antennas are comprised of long overhead wires, except that some ıadways and streams have underground conduits. The rights-of-way are brushed prevent antenna damage from wind-blown trees and to minimize any damage om fire. Tall timber is cleared 50 feet from either side of the antenna, th a minimum area of 30 feet cleared directly beneath the antenna (Zapotosky d Abromavage 1983).

F FIELDS AND ECOLOGICAL EFFECTS

Disturbance has always been a part of the natural systems of the world.

ural :atastrophes such as wildfire, wind storms, or drought can severely act the structure and functioning of ecosystems, but recovery is dictable. Only recently has human-related disturbance been imposed on the ironment. Man's utilization of the environment can cause disturbances that similar in impact to natural disturbances such as fires and windstorms. ever, many human-related disturbances appear to be unique. Radioactive lout associated with weapons testing, acid rain, CO_2 build up in the osphere, and the release of toxic chemicals as a result of energy-related ing, manufacturing, and electrical generation are examples.

The introduction of electric and magnetic fields into the environment as a ult of electric power transmission also introduces a potentially new turbation. It is becoming increasingly clear that electrical signals play important part in the organization and regulation of living organisms cker and Marino 1982). It is also clear that the biota of the world have lved in the presence of static electric and magnetic fields of about 0.12 m and 0.5 G, respectively (Eabry 1983), and that at least some organisms lize these fields to maintain proper orientation in the environment.

There has been a widely held opinion that power line related electric and netic fields should be considered harmless to native biota because these lds approximate those in the natural environment, except for areas located y near the line. This view is now being questioned. In fact it appears t the native biota may be more sensitive to artificial fields at field engths nearer to background levels than to substantially higher field engths. This concept is now thought of in terms of possible "windows" of ceived field strengths or frequencies where some organisms are particularly ceptive to electric and magnetic signals that are close to those of the ural earth fields (Adey 1981).

In this section, we evaluate recent literature to determine the likelihood t the presence of human-generated ELF fields will affect the normal ctioning of biota within their natural environment. We do not attempt to lude the extensive studies concerning cellular or tissue-level responses to ctric and magnetic fields or many of the laboratory-oriented studies except n the results can be clearly extrapolated to the natural environment. hasis is on studies since 1977.

AD-A156 942 ASSESSMENTS AND VIEWPOINTS ON THE BIOLOGICAL AND HUMAN HEALTH EFFECTS OF..(U) AMERICAN INST OF BIOLOGICAL SCIENCES ARLINGTON VA MAY 85 N00014-84-C-0446 4/5

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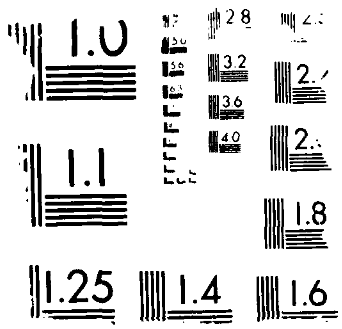
1.0
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1.8
1.25
1.4
1.6

Response of Individuals to ELF Fields

Here we consider how individuals may respond to electric and magnetic fields. Later sections will consider possible responses at higher organization levels.

Plants. Most studies designed to investigate the possible effects of ELF electromagnetic fields on plant growth have been concerned with electric power transmission facilities. The growth and productivity of crop plants common to the midwestern region of the United States were investigated near a 765-kV power line (Greene 1979, 1981; Hodges and Mitchell 1979; Hodges, Mitchell and Heydt 1975). They showed that electric fields that ranged from near background to about 20 kV had no effect on plant growth or productivity. The parameters studied included measures of seed germination, chlorophyll content, seedling heights and dry weights, and cell division. While statistical variability in the data was reported and statistical comparisons were made of plant growth responses in relation to the line, there was no attempt to estimate the size of the differences required before the particular research designs would assure detection.

Crop studies were also included as part of an investigation into possible environmental effects associated with a prototype 1100-kV transmission line in Oregon (Lee and Clark 1981; Rogers et al. 1980, 1982; Warren et al. 1981). During five years of study, no consistent differences were noted between treatment and control areas. Electrical field exposure values ranged from 7 to 12 kV/m, and both exposed and electrically shielded treatments were employed. An analysis of the statistical power levels achieved by the sampling design was calculated for these studies (Warren et al. 1981). These calculations showed a high probability for detecting differences between treatment and control groups. Comparisons were also made of pasture grass growth beneath the line and remote from it (Rogers et al. 1984) and revealed that electric fields up to 12 kV/m did not inhibit grass growth. Comparisons were made among study plots with electrical shields, simulated shields and no shields. Slightly greater growth was observed in plots that had simulated (nonconducting) shields; possibly indicating an influence of the shield on the microclimate. Endo et al. (1979) reported results of studies conducted in Japan where wheat plants were grown in 7.7-kV/m fields beneath an outdoor test line. They too reported no adverse effects.

Several studies have reported damage to trees growing close to power transmission lines (Miller and Kaufman 1978; Rogers et al. 1985; Zaffanella and Deno 1978). The damage described consisted of burned and dead needles and branches for tree parts exposed to intense electrical fields. This type of damage appears identical with that described by McKee et al. (1978, 1982) and Johnson, Poznaniak, and McKee (1979). In the laboratory, they exposed over 80 plant species to electric fields of up to 50 kV/m. Some species exhibited leaf tip damage at field intensities of 20 to 22 kV/m. The damage appeared to depend upon leaf-tip geometry; plants with pointed tips displayed damage at lower field strengths. Plants with rounded tips showed little damage except at very high (>50 kV/m) field strength levels. It seems clear, therefore, that there is little risk to plants growing near electric power transmission facilities. Normally, trees growing close enough to a commercial power line to be damaged by the intense electric fields would be removed as part of the construction and right-of-way maintenance activities (Lee et al. 1982).

Small Mammals. Numerous experiments have been carried out concerning the response of small laboratory mammals to electric fields. The reported effects have included reduced water consumption in rats and reduced size, as well as increased mortality, in mice (Marino and Becker 1977; Marino, Becker, and Ullrich 1976). Marino et al. (1979) also reported slower bone healing in rats. Phillips, Anderson, and Kaune (1981) reported a reduced rate of bone fracture repair in rats exposed to an electric field, but they noted that there was no permanent effect on bone strength. Rats given a choice were found by Phillips (1979) to spend more time outside of an area where the fields were greater than 90 kV/m. At field strengths below 50 kV/m, the rats spent the greater part of their time within the field areas.

It is unclear how results of laboratory studies such as those mentioned above might be extrapolated to animals inhabiting natural areas exposed to electric and magnetic fields. In some cases, the influence of such fields appears to affect the behavior of animals differently for different species, based on their varying sensitivity at detecting electric and magnetic fields or on physical characteristics such as the occurrence of whiskers and fur. (Waskaas 1981). Also small mammals typically inhabit areas in the natural environment that also contain some type of vegetation. As a result, they are largely shielded from the electric field associated with the overhead lines

(Lee et al. 1982). The possible effects of electric and magnetic fields on individual small mammals has not been investigated in the natural environment. On the basis of the laboratory studies and the natural shielding, it seems unlikely that individual small mammals would respond to overhead electric and magnetic fields. However, the effects on burrowing animals of electromagnetic fields present in the ground have not been investigated and may be another matter entirely.

Large mammals. Very little experimental research has been conducted to determine the likely effects of electric and magnetic fields on large animals in their natural environment. Those studies that have been conducted are mostly centered on domestic livestock. The effects of a 400-kV AC line on dairy cattle in Sweden were reported by Algers, Ekesbok, and Hennichs (1981), who analyzed fertility records of dairy herds pastured under a line. Two of the 38 herds studied showed decreased fertility for cattle pastured beneath the line, in comparison with controls. Those two herds spent more time beneath the lines and were serviced by farm bulls in contrast to the other 36 herds which had spent less time beneath the lines and had been artificially inseminated. Hennichs (1982) conducted a follow-up study using a larger sample. She reported no reduction in fertility in relationship to the line. However, the herds she investigated were all artificially inseminated.

Tests were conducted for several years concerning the response of cattle grazing within the vicinity of a 1100-kV prototype test line in Oregon (Lee, Bracken, and Rogers 1979; Rogers et al. 1982). In general, cattle showed no reluctance to graze or drink beneath the line, but there was a trend for decreased use of areas near the line during energized periods as compared to periods when the line was de-energized. No attempts were made to relate this response to either the electric field or audible noise components of the test line. There was no magnetic component.

Williams and Beiler (1979) conducted an investigation concerning the influence of a 765-kV power line on milk production in Ohio. They found no evidence that the lines had any overall effect on milk production. There was an increase in calf mortality and birth defects following construction of the line, but the average herd size was also changing during the study period, which may have confounded the study. Amstutz and Miller (1980) conducted a study to assess the health of livestock inhabiting areas near a 765-kV line in

Indiana. Their interviews with farmers and periodic inspections resulted in a conclusion that the health, behavior, and performance of the animals were not affected.

While there have not been any studies conducted concerning the behavior and well-being of individual large native animals, results from the livestock studies imply little likelihood of any effects. The only exception is the still unanswered question concerning the possible adverse effects on fertility as reported by Algers, Ekesbok, and Hennichs (1981).

Birds. Most of the work concerning birds and electric and magnetic fields has centered on ascertaining their sensitivity to magnetic fields. Birds might be expected to have the greatest need for a magnetic sense. During their annual migrations, they often fly long distances between their winter and summer grounds. Their ability to make these annual pilgrimages, day and night, during all kinds of weather, has long been a matter for speculation and wonder.

Evidence has been abundant for some time that static magnetic fields can influence the orientation, migration, and homing of several bird species, including European robins (Wiltschko and Wiltschko 1972), homing pigeons (Keeton 1971; Papi et al. 1978; Walcott 1974; and Walcott and Green 1974), and chickens (Clarke and Justesen 1979). The most definitive work has involved homing pigeons. Studies have utilized clock-shifted pigeons (birds raised under light and dark cycles out of phase with natural cycles), pigeons equipped with frosted lenses over their eyes, and pigeons carrying small magnets, brass weights or electric coils. Such research has been used to help determine how homing pigeons navigate. We now know that these pigeons have the ability to return to the loft without being able to see landmarks. They apparently do use the sun as a compass during bright days, but they can also successfully return to the home loft at night or under cloudy conditions. The use of attached magnets or electric coils was found to totally disrupt their homing abilities during cloudy days or when flying at night (Gould 1980; Keeton 1969, 1971; Schmidt-Koenig 1972; Visalberghi and Alleva 1979; Walcott 1974; Walcott and Green 1974).

We now know that several different types of organisms contain magnetic sensitive material in their bodies. Blakemore (1975) was the first to report on the occurrence of specialized areas of magnetite in bacteria. Since then,

biogenic magnetite has been found in a variety of organisms, including birds (Eabry 1983). Some of the recent findings concerning magnetite have been summarized by Maugh (1982) and Kirschvink and Gould (1981). Although the actual mechanism by which biota sense magnetic fields has not been clearly established, it does seem clear that at least some bird species can perceive electric and magnetic fields and that these fields may disturb their navigation systems.

Interestingly, little research has been conducted to determine the effects of ELF electric and magnetic f. .lds on native birds. It has been shown that manmade fields of similar magnitude as natural field strengths can interfere with the orientation of some migrating birds (Larkin and Sutherland 1977; Southern 1975), other birds such as hawks and eagles often use the towers associated with electric transmission lines for perching and nesting (Howard and Gore 1980). The developing young are exposed to electric and magnetic fields for substantial portions of their developmental periods, apparently without any detrimental effects (Lee 1980; Lee et al. 1982).

Fish. Apparently, some fish also possess the ability to detect weak electric and magnetic fields. The elasmobranch fishes (sharks and rays) are known to possess an acute sensitivity to magnetic fields and have been trained to distinguish the direction of the earth's field (Kalmijn 1966). The sharks and rays use their magnetic sensitivity to detect electric fields associated with their potential prey. It is not known whether they also use this sensitivity for navigational purposes (Gould 1980).

Both American eels and Atlantic salmon have been reported to be able to detect low-frequency electric fields of 7 to 70 mV/m, while low-frequency fields up to 20 V/m had little effect on the behavior of bluegill fry (McCleave, Albert, and Richardson 1974). Catfish have been reported capable of orienting themselves to an electric field based on the gradient of current density (Baranyuk 1979).

Invertebrates. Among invertebrates, it is not surprising that honeybees have received the greatest attention in terms of their sensitivity to electric and magnetic fields. There were several early reports of honeybees being adversely affected when placed near electric power transmission lines in Europe (Altmann and Warnke 1976; Husing, Struss, and Weide 1960; Warnke and Paul 1975; Wellenstein 1973). More recent studies in North America (Greenberg

and Bindokas 1981; Rogers et al. 1982) have confirmed that electric fields associated with transmission lines can affect honeybees. The effects noticed in both studies included excessive propolization within the hive, increases in the irritability and mortality of colonies located near the lines and poor survival of the colony over winter. Interestingly, these effects seem to be related to the flow of current through the hive. Even though hives are constructed from wood, there is a small but measurable induced current. The magnitude of this current is dependent on the height of the hives and local moisture conditions. Effects become noticeable when the induced current exceeds .02 to .04 mA (Rogers et al. 1982). It appears likely that the bees experience frequent shocks while inside the hive and that the resulting stress is responsible for the effects noted above.

Honeybees are reported to be even more sensitive in the detection of magnetic fields than homing pigeons (Gould 1980). It is not altogether clear what exact role magnetic fields play in the life of honeybees. Such fields apparently influence the construction of honeycomb in the hive. Worker bees will build comb in the same magnetic direction as that within the parent hives; however, strong magnetic fields are reported to disturb this pattern (Lindauer and Martin 1968, 1972). Another effect involves the ability of honeybees to set their circadian rhythms with the daily variations in geomagnetic field strengths (Martin and Lindauer 1977). Magnetic fields also appear to influence the orientation of the "waggle dance" that the bees perform on the honeycombs to direct other workers to food sources (Lindauer and Martin 1968; Martin and Lindauer 1977).

Honeybees as well as homing pigeons have surprising concentrations of magnetite in their bodies (Gould 1980). It is not at all clear that this material has anything at all to do with the apparent magnetic sensitivity of the honeybee, but research is continuing. Nor is it clear that the electric and magnetic fields associated with power lines or other current-carrying conductors in the environment adversely affect the behavior of honeybees. Honeybees have been observed to forage beneath a 1100-kV test line and to pollinate flowering plants located there in a normal fashion; however, this test line lacked the magnetic component (Rogers et al. 1982). There remains much to learn concerning the possible effects of electric and magnetic fields on the orientation, communication, and foraging behavior of honeybees.

Response at the Population Level

Almost all of the research concerning overhead transmission lines has been directed toward understanding the effects of right-of-way construction and maintenance activities on native plant and animal populations (Lee et al. 1982). Only rarely have the possible effects of electric and magnetic fields been addressed. Nevertheless, some studies have been conducted that provide insight to the possible influences of electric and magnetic fields on resident populations.

A study of deer and elk movement patterns was conducted in Idaho in relation to a 500-kV transmission line (Goodwin 1975). There were no apparent deterrent effects of the field on the migrating deer and elk; however, some animals were apparently attracted to the cleared right-of-way for feeding. The animals tended to avoid right-of-way areas in daylight hours during hunting seasons. Preliminary results of a study of a 500-kV line in Montana suggest that the use by elk of habitats near the line may have been reduced during periods of high audible noise resulting from corona discharge (J. Camfield, pers. com. 1985).

Studies of bird abundance near a 1100-kV prototype transmission line were conducted for six years in Oregon (Rogers et al. 1982). No significant trends in total abundance were detected. A census of small mammals present near the line was also conducted as a part of the 1100-kV studies (Rogers et al. 1982). No adverse effects of the electric field were found.

Griffith (1977) conducted a study concerning the ecological effects of a High Voltage DC transmission line in the shrub-steppe region of Oregon. He noted some differences in the abundance of wildlife near and remote from the line. Some bird species that were dependent on shrubs for nesting habitat or required a more closed habitat were more abundant within control areas as compared to the right-of-way beneath the line. Small mammal species that have an affinity for open or disturbed sites were more abundant on the right-of-way area. There were no differences in the indices of abundance (pellet groups) for mule deer or pronghorn antelope within the right-of-way or control areas.

Response at the Community Level

In general, there exists a paucity of information concerning the response of community-level parameters to electric and magnetic fields. This is

unfortunate in that information concerning any tendency towards changes in the size of dominant life-forms, reduction in species diversity, or changes in successional patterns would certainly provide additional insight as to the role of electric and magnetic fields as possible stressing agents.

Rogers et al. (1982) calculated diversity, evenness, and richness values for bird species occupying forested and shrub-dominated areas near a 1100-kV prototype in western Oregon. They showed that the distribution of bird abundance across species (evenness index) remained constant throughout the six years of study but that the number of species (richness) observed within both forest and shrub study areas changed from year to year. There were no changes in diversity, evenness, or richness as a result of the construction or operation of the 1100-kV test line, as determined through comparisons of results from treatment and control areas. The effect of electric fields on the growth form of Douglas fir, the dominant trees of the area, was also assessed as part of the study. Trees within 15 meters of the line displayed damage to the branches and buds in the upper canopy. As a result, the tree tops assumed a rounded appearance.

Response at the Ecosystem Level

No studies have been specifically designed to look at ecosystem-level parameters. Earlier approaches to ecosystem ecology regarded the ecosystem as a more or less closed system that occupied a limited area. In this respect, it would be difficult to decide just where to set ecosystem boundaries along electric and magnetic rights-of-way. The more recent concept of the ecosystem recognizes the futility of trying to set spatial boundaries for many study areas and that eventually a steady state would be reached for any sized ecosystem depending on environmental conditions (Margalef 1981). The critical experiments needed at the ecosystem level would be designed to show how the perturbations associated with construction and maintenance of electric and magnetic transmission systems affect the ecosystem, how these changes influence the return of the system to a semblance of its original condition, and any influence of the electric and magnetic fields.

CONCLUSIONS AND RECOMMENDATIONS

In this final section, we stress the need for further study. Some designs

for future research are presented. The general conclusion reached as a result of this review is that there do not appear to be any easily detected effects associated with the presence of electric and magnetic fields in the environment.

Effects of ELF Fields on Ecological Systems

We now know that many species of animals apparently have the ability to detect magnetic fields. However, it is not known how they integrate this information into their daily lives or how extraneous fields affect their normal patterns of behavior. It is clear that more information is needed concerning the effects of magnetic fields on the orientation and behavior of biota within the environment. The responses of biota to artificial fields near background levels and their abilities to detect alternating fields in comparison to the constant earth fields should be investigated.

Also uncertain is the extent to which electric and magnetic lines may be interfering with the normal breeding behavior of large animals or how these fields may be influencing their use of nearby areas. Investigations of this nature may have to be conducted on domestic animals and the results extrapolated to large native animals such as deer and elk.

Some species of fish clearly have the capability of detecting electric field intensities similar to those near some ELF facilities. The effects of these fields on their activities warrant further study.

While some information has been collected regarding the effects of electric and magnetic fields on ecosystem structure (e.g., abundance, diversity, standing crop), almost nothing is known about effects on ecosystem function (e.g., ecological energetics, resource cycling, or systems regulation). Most of the magnetic field studies conducted to date have viewed the fields as originating from point sources. The large land area encompassing the ELF communication system in Wisconsin and the elaborate powerline grids now existing throughout the United States make it feasible to conduct studies on the dynamics of ecosystems. Only in this way can any broad, cumulative stress be associated with the generation and transmission of electric and magnetic fields.

Research Designs

In general, the research designs employed during ecological field studies

do not appear capable of identifying effects associated with the electric and magnetic fields produced during operation of ELF transmission systems. We anticipate that such effects are likely to be subtle and probably long-term. Consequently, the research designs utilized for determining ecological effects must be structured for sensitivity to subtle changes over long time periods. Support for such studies has not been available; consequently, the critical experiments have not been conducted.

The principal biological response to any ELF transmission system is most likely to result from the installation activities and concomitant change in habitat conditions within the right-of-way. Conditions may be enhanced for some ecological parameters following clearing activities associated with line construction. We believe that the changing patterns of growth or consumer utilization of the cleared areas is a "confounding factor", and that the control/treatment type of design often employed in these kinds of studies may result in statistically significant evidence of a spurious effect (so far as the electric and magnetic emissions are concerned).

The best design for studies of this type would be one where the basic experimental unit consists of three different elements or treatments. One would need to be a segment of an operational line or a test line with electric and magnetic fields present; the second, an unchanged but matched control segment; and the third, a simulated treatment (e.g., a cleared right-of-way resembling the right-of-way as closely as possible but lacking any electric or magnetic fields). The control would permit documentation of changes due to clearing, while the simulated line would detect changes associated with the operational fields. There would, therefore, be two contrasts of interest during the final analysis. One would be a comparison of the operational line and the simulated line against the unchanged control. The other contrast would be between the simulated line and the electric and magnetic lines.

For some ecological study parameters, a control treatment-pairing (CTP) design may be adequate (Eberhardt 1976; McKenzie et al. 1977; Skalski and McKenzie 1982; Thomas, McKenzie, and Eberhardt 1981). If the parameter study areas are positioned within the electric and magnetic fields but remote from any right-of-way alterations, the CTP design would be suitable. This would only be assured for those parameters associated with species having little or no mobility. This design would be appropriate in studies of vegetation,

herpetofauna, small mammals, and some aquatic biota. This type of design has several advantages in analysis of a "no-effect" null hypothesis (Skalski and McKenzie 1982). Given a constant proportional relationship between control and treatment values, annual and seasonal (i.e., time-dependent) change may be removed when the study plots are well paired. The sensitivities for both the triplicate and CTP designs are dependent upon the intensity of sampling (L. L. Eberhardt, pers. com. April 17, 1982).

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in the incidence of malformations between generations and between the first and second breedings made it impossible to unequivocally conclude that there was a cause and effect relationship. They further suggested that any effect, if real, was probably secondary to maternal alterations.

Using induced current density and reproductive development chronology as scaling factors, this group of workers (Rommereim et al. 1985) subsequently performed further studies to see if chronic exposure of rats under a regime comparable to that used for swine would produce similar changes. The female rats and their offspring were exposed for 19 h/day to a 60-Hz, 100-kV/m unperturbed field (effective field strength about 65 kV/m). After 4 weeks of exposure, the F_0 females were mated to unexposed males during the period when the field was off; no significant developmental effects were detected in their litters. They were mated again at 7.2 months of age and their litters were evaluated shortly before term. The incidence of intrauterine mortality was significantly less in the exposed litters than in the sham-exposed litters, and there was a tendency toward an increased incidence of litters with malformed fetuses. When the female offspring were bred at 3 months of age, a statistically significant decrease in fertility was detected in the exposed group, and there was a significant increase in the fraction of exposed litters with malformed fetuses. This study employed a block design and, when the experiment was repeated under essentially identical conditions, no statistically significant between-group differences were detected. The authors stated that the difference between experiments might be attributable to random or biological variations but indicted that, alternatively, the results might suggest that--if there were an effect--the response threshold might lie at about the field strength used in the study.

The studies of Hansson and his collaborators are difficult to interpret in that quantitative comparisons have not been made available, and perhaps are flawed in that it appears that no attempts were made to obscure the identity of the groups to the observers doing the scoring. Nevertheless, Hansson (1981a, 1981b) described marked differences between both the microscopic and ultramicroscopic morphology of brains from control rabbits and those exposed in utero and during the first two postnatal months to about 14-kV/m electric fields from a powerline. Alteration of the large Purkinje cells seems to be the most consistent finding, appearing as lamellar bodies (altered granular endoplasmic reticulum) and altered cytoskeleton. These changes are

when water was available. The filial generation was born and reared to weaning outside the field; the offspring and their mothers were then introduced into the field. No effects on the fertility of the parents were detected, although their water consumption and growth of the females were significantly reduced. No effects on the development or growth of the offspring were detected, although much of their development took place before they were introduced into the field.

As indicated in several documents and reports, Phillips and his colleagues performed a broad screening study to detect effects attributable to electric field exposure in Hanford Miniature Swine. One group of swine was exposed to a uniform, vertical 60-Hz, 30-kV/m electric field for 20 h/day, 7 days/week throughout the experiment. A group of sham exposed swine was housed in a separate but environmentally-equivalent building. Evaluations of reproductive and developmental toxicology were included as part of this study (Sikov, Buschbom, and Phillips 1982; Sikov et al. 1985). The F_0 gilts were bred after four months of exposure. Some of the animals from both groups produced an F_1 generation of offspring; the other animals were killed for teratologic evaluation of their litters at day 100 of gestation. The incidence of teratisms in these litters (pooled across the prenatal and live birth studies) was similar in the exposed and sham-exposed groups. Prenatal mortality was less in the exposed than in the sham-exposed group. The F_0 females which farrowed the F_1 generation were rebred after 18 months of exposure and killed at day 100 of gestation. The malformation-incidence in the exposed litters (75%) was significantly greater than in the sham exposed litter (29%), but no consistent differences in litter size, fetal weight, or weight of fetal organs were detected.

The authors indicated that there were suggestions of impaired copulatory behavior and decreased fertility in the exposed F_1 gilts which were bred at 18 months of age, although the data are not completely convincing. Defective live and stillborn offspring were found in significantly more of the exposed litters than in sham-exposed litters. These F_1 animals were rebred 10 months later and teratologic evaluations performed on their second litters at day 100 of gestation. The percentage of litters with malformed fetuses was essentially identical in the exposed and sham-exposed groups. The authors indicated that there appeared to be an association between electric field exposure and developmental effect. However, they pointed-out that the change

a field strength of 80 kV/m on days 14 through 21 of gestation and evaluated the offspring postnatally. The numbers of control and exposed litters were small in both experiments, as estimated from the number of offspring which was used as the experimental unit for statistical analyses. The data suggested a reduced rate of growth, physical maturation, and sexual development. The statistical significance of the differences was not consistent across experiments and the interpretation may not have been addressed with adequate conservativeness. Nevertheless, the authors provide arguments that the findings are consistent with stress upon pregnant rats.

Experiments by Sikov et al. (1984) involved exposure or sham exposure of Sprague-Dawley rats for a 30-day period during one of three restricted periods of development. Uniform, vertical 60-Hz electric fields of 100 kV/m (unperturbed; 65 effective) were produced in a system in which spark discharges, ozone generation, or other artifacts associated with field generation were minimized. In the first experiment, the males and females were exposed for six days prior to and during a mating period; this exposure did not affect the reproductive performance of either males or females. Continued exposure of the mated females through day 20 of gestation did not affect the survival, size, or morphology of their fetuses. In the second experiment, prenatal/neonatal rats were exposed from the day of conception until the offspring reached day 8 of postnatal life; in the third experiment they were exposed from day 17 of gestation through day 25 of postnatal life. There were no systematic changes in the growth and survival of the offspring in any of these experiments. In the second experiment, the time of development of a few behavioral measures was slightly altered, but these few changes were not found again in subsequent experiments (described below) and so appear attributable to random variation.

In the study by Fam (1980), male and female ICR mice were exposed to a vertical, 240-kV/m (unperturbed), 60-Hz electric field. It was stated that all precautions were taken to prevent corona and ozone production, but the design for this study was limited by the ability of the animals to tolerate this field strength, as well as operational difficulties with animal husbandry--water could be made available for only one hour in the morning and the late afternoon. The parental generation was exposed for 22 h/day, for about 90 days. Following the initial three-month exposure, the animals were caged as breeding pairs and apparently mated during a 6-h field-off period

offspring exposed to the vertical field had decreased body weights in all three generations and a temporarily increased mortality rate relative to their controls. The body weights of the offspring of the first two generations of the horizontal field group were decreased relative to their controls, but those of the third generation were unaffected. The authors recognized that the configuration of their exposure apparatus was such that it is likely that the mice experienced appreciable grounding microcurrents ($\sim 1\ \mu A$) while they were eating or drinking. Although they suggested alternative explanations, it seems that their results may have been influenced by a response of the animals to the perception of these currents.

These workers (Marino et al. 1980) subsequently used both vertical and horizontal fields at a single strength, 3.5 kV/m, to expose mice of larger group sizes. Only incomplete and derived values are presented in this report so that it is difficult to evaluate the effects of exposure on mortality. Nevertheless, the authors claim that exposure to either a horizontal or vertical field increased preweaning mortality in the first generation of offspring. In the two subsequent generations preweaning mortality was increased by the vertical field but was not affected by exposure to the horizontal field. Postweaning mortality was increased by the vertical field exposures in the second and third generations. At some of the weighing periods the exposed offspring were significantly heavier than the corresponding controls. The authors proposed that the difference in the direction of the effect on weight in their two experiments and their inability to determine a cause for the observed mortality can be explained by a "generalized stress response." From the data presented, however, a conclusion of random variation is also tenable.

Seto (1979) performed a multigenerational study in which a parental and three filial generations of Charles River CD rats were continuously exposed to an electric field at a strength of 20 kV/km. A wide variety of morphologic, physiologic, and biochemical measures of effect were evaluated. No significant differences in the survival and growth of the filial generations were detected. Serum albumin levels were altered in the male offspring and there were a few sporadic changes in organ weights. They were not able to detect significant field-related effects during teratologic evaluations of prenatal litters from rats of the third generation.

In two pilot experiments within the same study (Seto 1981) exposed rats to

although it was indicated that one worker found a trend similar to that reported by Delgado et al. (1982). However, an independent evaluator who visited their laboratory (Rozzell 1984) concluded that the results were valid and that the apparent unreproducibility resulted from a dependency on the orientation of the eggs during the exposure period, as reported by Leal et al. (n.d.). Thus, if this phenomenon is real, it would represent a unique relationship of biophysical interest, but it would seem to have little relevance to the development of mammalian embryos where maternal and fetal orientations change at frequent intervals.

STUDIES IN MAMMALIAN SYSTEMS

Electric Field Exposures

There have been a few reports that exposure of prenatal mammals to 60-Hz electric fields produced deleterious effects on postnatal growth and survival. None of these results have been unequivocal and it does not appear that there have been independent verifications or replications of the findings. The studies dealing with reproductive and developmental effects include that of Knickerbocker, Kouwenhoven, and Barnes (1967) who chronically exposed male mice to a 60-Hz, 160-kV/m (unperturbed) electric field for an average of 6.5 h/day, 5 days/week for 10.5 months. Although there was not a continuous corona associated with the animals at this field strength, transient coronas occurred when the mice reared in their cages, and minimal levels of coronas and ozone could be detected at the corners and edges of the electrodes but not within the cages. These males were bred to unexposed female mice during the period that the field was not energized. A transient decrease in fertility was observed after two months of exposure; this finding was not obtained again in a second experiment performed to examine this time period. The growth curves of the male progeny were significantly depressed relative to the progeny of control mice, but the growth curves of the female progeny were unaffected. The authors suggested that this apparent effect might have been attributable to the location of the cages relative to windows in the housing facility rather than represent an electric field effect, per se.

In a pilot study, Marino, Becker, and Ullrich (1976) exposed both male and female ICR mice continuously to 60-Hz electric fields over three generations of progeny. There were two exposed groups--one in a 15-kV/m vertical field and another in a 10-kV/m horizontal field--in addition to controls. The

being exposed continuously to 60-Hz electric fields at one of several nominal strengths up to 100 kV/m, or were incubated without exposure. Other eggs were removed from the exposure system after 19 days of incubation to allow evaluation of the chicks after hatching. They were unable to detect consistent dose-dependent differences for any of the measures used which included: mortality, malformations, body weight, and metatarsal length. Measures of simple reflexes and behaviors also failed to detect effects attributable to electric field exposure.

Essentially negative findings were obtained in several experiments by Veicsteinas et al. (1985), who measured fertility, egg hatchability, growth, and malformations after prolonged exposure of chickens, eggs, and chicks to electric fields at strengths up to 15 kV/m for 20 h per day.

Magnetic Field Exposure

Most of the limited literature available (see Mahlum 1977 for review) regarding the developmental effects of exposure to magnetic fields deals with static or DC fields and, thus, is not directly related to considerations of the potential for effects attributable to ELF AC fields. The few studies with AC fields include those of Krueger et al. (1972) who exposed chicks from 0 through 28 days of age to a nonuniform, 45-Hz, 1.4×10^{-4}T magnetic field. They found that this significantly decreased growth rates but did not affect viability or activity. None of these measures were changed by exposure of chicken eggs throughout incubation to magnetic fields in the 45 to 75 Hz frequency range, at intensities between 10^{-4} and 3×10^{-3}T.

Substantial interest was generated by recent reports of Delgado et al. (1982) that they had detected marked malformation effects in chicken eggs exposed to relatively low levels (0.12×10^{-6} to 12×10^{-6}T) of pulsed (10 to 1000 Hz repetition frequency) magnetic fields on the center axis of a cylindrical coil activated by a physiological stimulator. They subsequently reported (Ubeda et al. 1983) that the wave shape of the pulse was an important determinant of whether or not there was an effect and that some stronger fields were without effect, while still others reduced malformation incidence below control levels. As indicated in newsletter reports (Microwave News March 1983, June 1984) there has been some skepticism as to whether the anomalies may have represented slight developmental delays. These sources reported that a number of attempts to replicate this work were unsuccessful,

conditions where the likelihood of coupling of the field and induction of currents in the developing organism are maximized.

STUDIES IN NON-MAMMALIAN SYSTEMS

Electric Field Exposures

Some of the studies in avian species were reviewed by Sheppard and Eisenbud (1977) who discussed experiments which sought to determine whether developmental processes in birds were affected by electric and/or magnetic fields. The studies dealing with exposure to electric fields include the experiment of Krueger et al. (1972) who exposed chicks to nominal 60-Hz, 3.4-kV/m or to 45-Hz, 3.6-kV/m fields generated under conditions so as to produce marked variations in field strength throughout the exposure volume. Exposure during the period between hatching and 28 days of age did not significantly affect viability, behavior, or activity levels. However, these exposures did result in a slight, but not statistically significant, decrease in growth rates. Durfee et al. (1975) exposed chicken eggs during incubation and continued posthatching exposure of the resulting chicks through four weeks of age. The parallel plate system produced vertical fields with ranges in field strengths from 0.001 to 3.6 kV/m and frequencies from 45 to 75 Hz. No statistically significant differences were detected for any of the several measures.

Graves and his colleagues (1978a, 1978b) demonstrated that pigeons could perceive 60-Hz electric fields at strengths above 32 kV/m. They also found (Graves et al. 1978b) that daily 30-min exposures of chicks to 60-Hz fields of 40 or 80 kV/m on days 1 to 22 posthatching significantly reduced their gross motor activity, measured in daily one-hour sessions during the week following removal from the field. Exposure for three weeks to fields of the same intensities produced a statistically significant, but transitory, enhancement of early growth in male chicks and a similar, but smaller, effect in females. Although it was not possible to make recordings during exposure, measurements taken after removal of the chicks from the field indicated that neither short- nor long-term exposure to the highest field strength affected heart rate or the electroencephalogram. These authors (Graves et al. 1978b) did not detect effects on viability, growth, or development.

More recently, this group (Reed and Graves 1984) reported on two comprehensive series of experiments in which chicken eggs were incubated while

through direct effects on the developing embryo, fetus, or neonate or whether their origins are indirect. Such indirect effects could be mediated through changes in the reproductive or endocrine system of a parent prior to conception or of the dam during gestation or lactation.

In this regard, it may be useful to reiterate the general concept that essentially all physical agents (including electromagnetic fields per se and via secondary phenomena) can be perceived by mammalian organisms and elicit biological responses. Many of these responses are in the usual repertoire and are appropriate responses for the species; it therefore is necessary to distinguish between physiologic and toxicologic responses to such stimuli. In addition, an extensive literature has developed on the effect of perinatal stimuli affecting the maternal behaviors of the dam on the well-being and physiological responses of the offspring in later life. This literature will not be reviewed here, but the concepts may be relevant to the interpretation of the few mammalian studies in which suggestions of deleterious effects on postnatal measures have been noted.

Information regarding direct effects of physical agents on intrauterine development can often be quantitatively extrapolated, with appropriate scaling, from animal studies to human populations. However, pregnant women are routinely subjected to a wide variety of psychological and physical stimuli so that effects mediated through a response to a novel--but not inherently noxious or toxic--stimulus in an animal system may not have relevance for extrapolation or for formal risk analyses. On the other hand, such effects may be of importance in establishing the field strengths and associated territorial boundaries that might be established to control inadvertent exposures of populations of economically and/or aesthetically important species of animals.

A number of studies have investigated the responses produced by electromagnetic field exposure in birds and in other inframammalian systems, as well as in a variety of in vitro systems. The few positive results may have relevant developmental implications in the sense of suggesting susceptible biological processes, although the basic physical and biophysical interactions obviously will be different under these circumstances than they would be in a mammalian embryo in vivo. However, the results from such studies may provide indications of whether or not direct effects, i.e., those not mediated via a maternal mechanism, can be produced under "worst-case"

REPRODUCTIVE AND DEVELOPMENTAL ALTERATIONS
ASSOCIATED WITH EXPOSURE OF MAMMALS TO ELF (1-300 Hz)
ELECTROMAGNETIC FIELDS

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INTRODUCTION

A number of studies have indicated that developing stages of many animal species, including prenatal and neonatal mammals, are generally more sensitive to injury by exposure to various physical and chemical agents than are more mature life stages (Mahlum et al. 1978). Although not all agents are more toxic to prenatal and neonatal mammals than to their dams or to adults of the same species, the greater sensitivity--when it is present--is thought to originate from the multitude of interacting intracellular and intercellular developmental processes and to the variety and number of finely tuned regulatory processes which may be affected by subtle perturbations. The possibility that there may be unique sensitivity during prenatal and postnatal development suggests that quantitative evaluations of developmental effects may provide responsive systems for detecting toxicity. Moreover, these considerations strongly indicate that a full assessment of the potential hazard associated with ubiquitous occupational or environmental agents to which pregnant women or children may be exposed should include reproductive and developmental evaluations.

The primary goal of this report is to summarize and analyze the effects associated with exposure of developing mammals to electromagnetic radiation in the extremely low frequency (ELF) range (i.e., 100 to 300 Hz). Since reproduction and development are linked in the practical sense, as well as through their physiological relationships, effects displayed as reproductive impairment--which can not always be distinguished from embryotoxicity--also will be considered.

If, in the final analysis, it appears that in vivo exposure of mammalian systems to ELF electromagnetic energy produces effects on prenatal or postnatal development, it would be important to establish whether they arise

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accompanied by an increased number of glial cells, with a degree of regional specificity. In their more recent studies (Hansson, Darnfors, and Rozell 1985), rats, mice, and rabbits were exposed to 10-kV/m fields during gestation and the first four postnatal weeks, for 22 h/day, 7 days/week. They indicated that similar morphological findings were obtained in these experiments, although data have not yet been provided as a written manuscript.

Cerretelli et al. (1979) have performed extensive studies using electric fields generated between two steel plates separated by a variable distance. By varying the caging, animals of several species (including mice, rats, rabbits, and dogs) have been exposed to vertical, 50-Hz fields at strengths up to 100 kV/m for up to two months, with exposure time ranging from 30 s to 8 h/day. Male rats were exposed at the highest field strength (100 kV/m); either daily 30-min exposures for 55 days or daily 8-h exposures for 48 days were used for durations up to two months. Neither the libido nor the fertility of the exposed males was affected relative to controls, as determined by the number of copulations with unexposed females or the fraction of these females becoming pregnant. Teratologic evaluations of the litters resulting from these matings disclosed no morphologic differences attributable to the exposures, although fetal weights were reported to be significantly less than in those sired by controls. Serial evaluations of semen did not disclose any changes in the morphology, mobility, or vitality of the spermatozoa, and no gross physical or histologic abnormalities of the testes were detected.

Magnetic Field Exposures

In one study, Ossenkopp, Koltek, and Persinger (1972) exposed pregnant rats to a 0.5-Hz rotating field (0.5×10^{-4} to 15×10^{-4} T) during various periods of gestation and studied the offspring after birth. The weights of the thyroid gland and the testes were greater in the exposed than in the control offspring, although body and adrenal weights were unaffected. A number of behavioral measures were altered. This is in accord with this group's previous report (Persinger 1969) that the exposed offspring exhibited less activity than controls in an open field. Likewise, the exposed offspring were more responsive when tested using a suppressed response paradigm (Persinger and Pear 1972).

Fam (1981) studied the effects of 1-week, 23-h/day exposures of male ICR

mice to a 60-Hz, 0.11-T magnetic field produced by an electromagnet. The mice could only be exposed singly while enclosed in a plastic capsule, with controls housed in an identical capsule located elsewhere in the room. Group sizes were small (N=9) and environmental conditions were not held equivalent. "Reproductive ability" was evaluated in one exposed and one control mouse and no effect was found. Most other evaluations, other than body weight and water consumption, were also unaffected.

Combined Electromagnetic Field Exposures

Coate et al. (1970) performed chronic exposures of female rats and their progeny to a combined electric and magnetic field (10 or 20 Vm, 1 or 2×10^{-4} T, 45 or 75 Hz). The parental animals produced a filial generation which was raised to maturity and, in turn, produced an F_2 generation that was raised to weaning. The results suggested that the fertility of the parental animals may have been slightly--but not significantly--decreased. Preweaning survival was low throughout the study--presumably due to the animal-housing arrangement. This detracts from any possible importance of the finding that the survival of the F_2 offspring was significantly increased.

A group at the Swedish University of Agricultural Sciences (Algers, Ekesbo, and Hennichs 1981; Hennichs 1982) has maintained a continuing surveillance of herds of cows maintained under 400-kV transmission lines and herds in surrounding areas. They observed that in the two herds with the maximum number of days grazing under the lines that there was a decrease in fertility following activation of the lines. Since the time period was relatively short, the authors conservatively refrained from drawing conclusions about causal relationships and indicated that they had not yet ruled out other possible reasons for the change in fertility.

Based on survey data and semi-subjective classifications of field strengths, together with a variety of inferences, Wertheimer, Fulton, and Leeper (1985) have concluded that the 60-Hz electromagnetic fields may adversely affect fetal development. Based on a failure to find increased childhood cancer with presumably greater prenatal exposures, they concluded that the exposures led to an increased abortion rate. They also concluded from case-control studies, seasonal shifts in sex ratios, and surveys of waterbed and electric blanket users that prenatal electromagnetic field exposures are associated with perinatal and congenital defects. From comments

by epidemiologists and general inspection of the data, this reviewer remains unconvinced that Wertheimer and colleagues have made their case.

Nordstrom, Birke, and Gustavsson (1983) have reported on a retrospective evaluation of fertility and reproductive outcome among workers at high voltage substations. Data were obtained from survey questionnaires and inspection of hospital records. Although issue can be taken with their selection of a control groups, bases for matching, categorization of outcomes, etc.,* the primary finding was that the frequency of "normal pregnancy outcome" is reduced in the population actively involved in working in high voltage switchyards, and that this was due to an increased incidence of congenital malformations. They also found that couples had greater difficulty in conceiving when the male was employed at a high voltage substation.

This latter observation is in keeping with that of Knave et al. (1979), who also found that comparable workers had fewer children. Unlike Nordstrom, they indicated that the difference was present before beginning work in that environment and was related to a higher education level in these workers than the control population. This report further serves to place the situation into perspective since it presents reasonable estimates of exposure levels and time but--more importantly--points out some of the ancillary factors, such as fear and apprehension, which can have a greater reproductive impact than the presumed electromagnetic exposure.

DISCUSSION

There have been no studies which clearly demonstrate deleterious effects of ELF electromagnetic field exposures during either prenatal or postnatal development of any mammalian species. Nevertheless, it seems that findings suggestive of such effects appear with a frequency that perhaps is greater than should be attributed to chance, although it should also be noted that an interplay of various biases may be involved. Accordingly, it would be most conservative to conclude that a high incidence of deleterious effects is not readily produced under the circumstances which have been studied, but that the possibility that common occupational or environmental exposures may produce measurable effects must remain open for consideration.

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*These are problems common to epidemiologic studies and will not be addressed here. Suffice it to say that these problems can affect the validity of the conclusions.

Based on the relationships indicated above, especially the paucity of reported effects from embryonic exposure in non-mammals other than under circumstances which provide unique opportunities for field-tissue interactions, it seems highly unlikely that electromagnetic fields have direct effects on the mammalian conceptus. Thus, if there are effects produced by prenatal exposure to electromagnetic fields, it seems most likely that they are secondary to maternal changes related to her perception of the fields. Such changes in the dam, which may affect her maternal behavior toward her offspring (as well as perception-related changes in the neonate), could play a role in any effects produced by exposures during postnatal development.

There is an adequate body of information to justify accepting the hypothetical possibility that such secondary mechanisms may exist, but certainly not enough to make a convincing argument for their existence. A number of investigators have demonstrated that electromagnetic fields in the strength-range used in many of the studies summarized above can be perceived by the relevant experimental species, e.g., Hjeresen et al. (1980) and Lovely and Phillips (1985). Some workers, e.g., Marino et al. (1980) and Seto (1981) explained the patterns of change found in their experiments on the basis of stress theory. While this may not be applicable in all instances, an open mind must be maintained toward the potential for stress and adaptation relationships when novel stimuli are perceived by experimental animals. Such perception may be involved in the changes in the neurochemical patterns associated with pineal glands as reported by Wilson et al. (1981) and the production of an arousal response in mice exposed during the inactive phase of the circadian cycle (Rosenberg et al. 1983). It is possible that changes of these sorts could lead to a dyssynchrony between estrus, ovulation, and fertilization and, thus, increase the likelihood of developmental derangements.

Superimposed on these possible interactions are the various indications of electromagnetic field induced changes in reproduction-related and adrenal hormones (Free et al. 1981; Marino et al. 1979) and their potential effects on prenatal and postnatal development as well as on reproduction. Thus, one must accept the possibility that there are operational mechanisms by which reproductive and developmental toxicity can be induced through exposure to electromagnetic fields.

As indicated above, however, there is no strong evidence that such a sequence of interactions does, in fact, occur and--if it does--whether the

phenomenon has relevance for exposures of women or children. Even exposures of males or females prior to pregnancy may give rise to various indicators of infertility, embryotoxicity, or neonatal deficits via secondary mechanisms. Moreover, as was noted above in describing the study of Knave et al. (1979), psychological factors are apt to play important roles in the responses of human populations, although it certainly will be difficult--if not impossible--to distinguish between differences attributable to fear or apprehension from those resulting from perception and subtle direct effects.

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BEHAVIORAL EFFECTS OF EXTREMELY LOW FREQUENCY ELECTRIC AND MAGNETIC FIELDS

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Behavior depends on a variety of factors: (1) structural and functional characteristics common within a species; (2) behavioral and other organismic consequences of prior exposure to specific environments including, but not limited to, a specific factor of interest; and (3) the current state of the environment. A measure of behavior depends not only on those factors but also on the method of measurement itself. It is important to recognize that the name of a measurement method is not the same as the specification of the values of the parameters that comprise the measurement technique.

In this paper we review the behavioral consequences of exposure to low-frequency electric, magnetic, or combined (EM) fields, emphasizing reports published between 1977 and 1984 in the power line frequency range of 50 to 60 Hz. Although we recognize that other results have been discussed at meetings or summarized in abstracts, we cannot review them until detailed accounts are published, preferably following peer review.

This examination seeks to identify behavioral effects and relate them to both behavioral and exposure parameters. Parameter values cited in this report are those specified in the original reports. We do not attempt to scale these values across species. The ability to identify mechanisms and interpret exposure effects in terms of their hazard (or as indices of toxicity) depends on not only obtaining behavioral information, but also understanding the information's functional significance and relation to other consequences of exposure. We recognize that a behavioral reaction need not be indicative of a direct modification of either the peripheral or central nervous system by the factor being studied. An agent can produce behavioral effects in a variety of ways with multiple actions occurring at the same time. A comprehensive characterization of an effect requires evaluating all of these factors.

Our approach in this report is based on our backgrounds in experimental psychology, including the experimental analysis of behavior, behavioral pharmacology, behavioral toxicology, and on our own experience in the laboratory study of the behavioral effects of 60-Hz electric fields. Based on many recent studies, we conclude that one way transmission line frequency (50- or 60-Hz) electric fields can affect behavior is by functioning in a fashion equivalent to other peripheral stimuli to which an organism may be sensitive, particularly vibrotactile stimuli. Such stimuli can produce reactions which are crucially dependent on stimulus parameters, especially intensity, as well as on relationships between the behavior and the stimulus, and on the prior history of exposure to identical or similar stimuli.

ELECTRIC FIELDS

Detection (Perception) Experiments

Detection means the subject can discriminate between the presence and absence of a condition, a state, an event, or a stimulus. The detection response measured by the experimenter can be arbitrarily selected. The response should not be elicited by the stimulus, nor should its occurrence be controlled simply by its effect on the stimulus. Although the discrimination need not be perfect, the experimenter-defined "detection response" (also called a "correct detection," a "hit," or a "report response") must occur with a greater probability in the presence of the stimulus, or signal, than in its absence. Such a definition does not require that the subject be able to describe the stimulus; e.g., a human observer might be able to discriminate between the presence and absence of an EM field and yet not be able to provide a description of a sensation associated with the presence of the field.

Threshold is a term used in different ways in the electromagnetic as well as other literatures. A reviewer must determine how the term is defined for each experiment (not just behavioral experiments) if appropriate comparisons are to be made. "Threshold" is defined, in general terms, as the onset or very beginning of an event. Our interest is usually in determining the minimal conditions necessary to produce that event or effect.

The relationship between the values of a stimulus parameter and the probability of detection is described by a psychophysical function. A particular psychophysical function of interest is the relationship between detection and field strength (or intensity) when other parameters remain

constant. Duration of exposure is another parameter of interest. Frequency and waveform of the stimulus also have been implicated in EM research.

Detection thresholds and psychophysical functions must be determined for several reasons. First, these functions themselves pose questions; posited mechanisms of action must be able to account for the observed functions. Second, as a corollary, such data may guide the search for mechanisms. Third, if the conditions necessary to produce one effect, in this case detection, are sufficient to produce a second, then the role of detection in determining the second effect must be evaluated.

Detection may be the most sensitive and reliable response to powerline frequency electric fields that has been shown within and across species. Detection has been documented in the literature for humans (Cabanes and Gary 1981; Deno and Zaffanella 1975; Kouwenhoven et al. 1966, 1967; Reilly 1978), rats (Stern et al. 1983), and pigeons (Cooper et al. 1981; Graves 1981). Some fishes are known to be extremely sensitive to EM fields (e.g., see review by Bullock 1982); however, we shall not review that literature here. Some reports of other effects of exposure did not explicitly study detection, but the field strengths required to produce those effects were most likely sufficient to produce detection of the field. These include increased motor activity in deer mice (Rosenberg, Duffy, and Sacher 1981; Rosenberg et al. 1983) and rats (Hjeresen et al. 1980), and escape from or avoidance of the field by rats (Hjeresen et al. 1980; Sander, Brinkmann, and Kuhne 1982) and miniature swine (Hjeresen et al. 1982).

The Cabanes and Gary (1981) report provides a detailed, though incomplete, description of the sensitivity of humans to 50-Hz electric fields. Seventy-five volunteers walked through a large room where the strength of the field depended on location. Field strength varied between 0.3 and 27 kV/m. At each of 24 locations, a subject reported on a questionnaire if he or she could detect the field and, if so, the nature of the sensation.

Although the report does not show individual psychophysical functions nor a measure of individual thresholds (as conventionally defined in classical psychophysical experiments, e.g., Engen 1971), it does provide a useful general description of the sensitivity of clothed humans who walked through a powerline frequency electric field under fair weather conditions. First, there were large individual differences in detection sensitivity to the field, with a small percentage of subjects perhaps detecting fields at or below 2 kV/m

and yet 50% not detecting the field at 27 kV/m. Second, orientation of the subject within the field affected detection. More subjects detected the field if one arm was stretched horizontally than if both arms were at their sides; even more detected the field if one arm was raised above the head. Third, some subjects reported sensations of tingling or vibration. Fourth, sometimes the sites of sensation were at the boundaries between skin and clothing or other material in contact with the skin. Fifth, rubbing exposed skin with plastic or nylon material increased the magnitude of the sensation. Sixth, at the highest field strength studied, most of the subjects detected the field if an arm was raised, with about 10% reporting "unpleasant shot" types of reactions.

In a second set of observations, one of the authors placed his forearm into an apparatus that produced a local field up to 100 kV/m. The author reported detecting the field prior to, but not following, shaving the hair off the arm.

The Cabanes and Gary (1981) report provides a description of human perception of powerli e frequency electric fields that seems consistent with other available reports. Although the experimental design was an improvement over many of the earlier, more casual approaches, several limitations in design preclude considering this a definitive analysis of either the human threshold or the mechanisms of detection. First, each subject was asked to report only once at each location (i.e., at each field strength). Second, the questionnaire may have biased the subject towards reporting only if a definite vibrotactile-like sensation occurred. Other, perhaps less well-defined sensations might well have gone unreported. Third, each subject was constantly exposed to an electric field with variation in strength occurring as the subject followed the specified path through the field. If exposure to the field itself modifies sensitivity to fields, such action would have influenced the results. Fourth, clothing characteristics were implicated as a variable that influenced reactions to the field, but apparently no attempt was made to control type of clothing worn. This could have influenced variability within and between subjects.

Results from the second experimental design, in which the forearm was exposed, are interesting, but they should be viewed as preliminary. The only subject was one of the authors. The report does not indicate whether the subject knew when the field was on or off. Only one portion of the body was

studied under the treatment of hair versus no-hair. Although the preparation is a potentially useful one, more carefully designed experiments are required before we can express confidence in the conclusion that hair may be necessary for detection.

Stern et al. (1983) reported the detection sensitivity of male Long-Evans rats to 60-hz electric fields. A rat was confined by a small plastic chamber located on one plate of the exposure system. To start trials lasting a few seconds, the rat--partially deprived of food--was trained to press a small lever in the absence of the field. If the field was turned on during a trial, pressing of a second lever would occasionally produce a small pellet of food. Those presses were the "detection" responses. Field strength was varied randomly across daily training sessions. Psychophysical functions were produced that showed the relation between field strength and proportion of trials with a detection response. Use of sham and control trials both provided an estimate of detection responses not controlled by the electric field and demonstrated that the field generating system did not produce artifacts controlling the detection responses. The threshold of detection, i.e., the field strength required for detection with a probability of 0.50 (after correction for "false alarm" or "error" detections occurring during sham and control trials), was calculated. Thresholds generally fell between 4 and 10 kV/m for the 19 rats studied. It is important to recognize that many of the rats reliably detected the field even at 2 kV/m, albeit with a lower probability of about 0.05. (The findings were replicated with female rats by Stern and Laties (1985).)

With respect to detection, there are some potentially important differences between the work with humans and that done with rats. First, the data obtained from the rats were based on repeated observations following extensive preliminary training, whereas data from humans was more limited and did not involve explicit training with feedback about accuracy. Second, onset of the field was essentially instantaneous when a trial started for the rats and the field strength remained constant, but the humans were exposed continuously to a field that varied in strength as they moved through the field. Third, the payoff function was explicitly defined for the nonvolunteer rats but not for the volunteer humans. In addition, the food payoff was obviously exerting strong control over the detection behavior of the rats. With comparable influences we suspect that humans could detect fields at

:chanisms, as well as eliminate nonproductive speculative accounts. Those ıtcomes, in turn, would provide some of the information sought by agencies ›ncerned with possible hazards associated with exposure to EM fields.

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100 V/m; 75 Hz, but not 45 or 60 Hz, at 56 V/m; and also for 60 and 75 Hz at 100 V/m. More carefully designed experiments are required to increase our confidence in those observations. However, we should note that the general form of the IRT distributions remained intact. If the general exposure had any effect, it did not produce a general debilitation in responding.

Since a few reports indicated that EM fields affected "reaction time" and interresponse-time schedule-controlled behavior, some investigators or reviews concluded that such exposures affected some aspect of "timing behavior" or "subjective estimates of the passage of time" (e.g., National Academy of Sciences 1977; Persinger, Ludwig, and Ossenkopp 1973; Sheppard and Eisenbud 1977). To the extent that the procedures are called timing-behavior procedures such a statement is simply a tautology. On the other hand, to the extent that the statement implies an assertion that behavioral or neural processes fundamental to "timing" are involved, the conclusion is not particularly meaningful, even if the observations are confirmed. Those reports or reviews do not define "timing" or "timing behavior." The implied concept is oversimplified at best. A similar concern was expressed several years ago (de Lorge and Marr 1974); however, those comments have gone unheeded. A recent conference of the New York Academy of Sciences (Gibbon and Allan 1984) reviewed some of the complexities of current approaches to the analysis of temporal control.

FINAL COMMENTS

The number of studies examining the effect of ELF electromagnetic fields on behavior is small. Behavioral and exposure parameters generally differ greatly among them. Obviously an exhaustive mapping of the procedural space is not viable. We believe it would be useful for reports to specify reasons for selecting the particular parameter values of the study. Were they based on clearly defined requirements of funding agencies, theory, prior observations, convenience, limitations of access to facilities, or perhaps arbitrary decisions.

Whenever an effect is identified, in either humans or nonhumans, it should be studied thoroughly by varying both exposure and behavioral parameters systematically, both within and across species and also across laboratories. Such a programmatic approach would provide the data required to confirm the original observations, identify boundary conditions, and evaluate proposed

We share some of these concerns and feel that the evidence warrants our suspending judgment as to the validity of some of the earlier studies reporting low level effects. In some instances reported effects may be due to experimental errors, confounding variables, or chance outcomes. On the other hand, the absence of a common result across some of those experiments cannot prove the absence of an effect; we must continue to remind ourselves that we cannot prove the null hypothesis.

In addition, some apparent differences in outcomes may be called "differences" or "conflicting results" because a common name was used for procedures varying widely in character or parameter values. Several studies, for example, examined the effect of EM fields on "reaction time." There were numerous and potentially important differences in parameter values across the behavioral procedures; however, details are often lacking in those reports. The stimuli, the responses, and the payoffs differed. Differences in those variables are known to affect the results of reaction time studies (e.g., Teichner 1954; Teichner and Krebs 1972). Clearly there was no single "reaction time" procedure used across those studies. Human subject studies include Beischer, Grissett, and Mitchell (1973), 45 Hz at 1 G; Friedman, Becker, and Bachman (1967), 0.1 or 0.2 Hz at 5 to 11 G; Hamer (1968), 2, 6, and 12 Hz at 4 V/m; Hauf and Wiesinger (1973), 50 Hz at 1 and 15 kV/m; and Konig (1974), 3 and 10 Hz at 1 to 2 V/m; and nonhuman primate studies summarized by de Lorge and Grissett (1977), 0.3 mT at 7 or 45 Hz with E fields less than 20 V/m; and de Lorge and Marr (1974), 7 and 45 Hz at 3 G and 10, 45, 60, 75 Hz at 10 G and 7.4 V/m. Along with those differences, exposure durations differed across the experiments.

Another characteristic of these studies that contributes to our difficulties in evaluating them is the general absence of careful, systematic work that not only identifies an effect but also maps functional relations among variables--including the behavioral ones. Olton (1983), albeit in a different context, amplifies our concern about the need for such data in order to evaluate how a treatment variable affects a behavioral process.

Another source of concern or confusion found in the earlier literature is the series of studies reported by Gavalas et al. (1970) and Gavalas-Medici and Day-Magdaleno (1975, 1976), which indicated that low strength electric fields altered interresponse-time distributions of monkeys responding under an IRT schedule of reinforcement. Effects were reported for 7 Hz at 10, 56, and

averaging 1.7 mWb/m^2 (rms) might have produced increases in motor activity of groups of DBA/2J and CD/1 male mice. An exposed unit, called a "squad," consisted of three mice. Each squad was housed in a plastic exposure cage that rested on a motion detector. The cage was located inside a hollow polyethylene cylinder with a coil wound around it. Six minute observation periods occurred intermittently over a single 48-h session. Gross locomotor activity was recorded during consecutive 2-min blocks--before, during, and after exposure. Activity levels were greater during the exposure periods. The authors attempted to eliminate or at least record the presence of variables potentially confounded with the magnetic field exposures. Nevertheless, they expressed continued concern that some such subtle variable might have been operating. It would be useful to have independent replication using other exposure systems coupled with the use of more adequate devices to measure environmental parameters.

EARLIER REPORTS OF EM FIELD EFFECTS

We neither list nor review in detail experiments reported prior to 1977 that examined possible behavioral effects of low-frequency EM fields. That information is available in several sources including the following reviews: de Lorge and Marr (1974); Konig (1974); Lee et al. (1982); National Academy of Sciences (1977); Persinger, Lafreniere, and Ossenkopp (1974); Persinger, Ludwig, and Ossenkopp (1973); Sheppard and Eisenbud (1977); and Scott-Walton et al. (1979). Many of the earlier studies examined electric fields at frequencies below the 50 or 60 Hz of powerlines and at field strengths on the order of V/m rather than kV/m. In addition, several studies examined magnetic fields, sometimes along with the electric field. Our overview of this literature provokes the following reactions. First, studies reporting positive effects generally did not manipulate parameters to determine boundary conditions. And second, those studies reporting negative effects generally failed to manipulate parameters until either positive effects were found or a wide set of conditions could be specified to be without effect. This situation, in part, seems to have rendered the National Academy of Sciences' Report Committee unable to draw firm conclusions about many low frequency, low level effects; instead the report indicated that "the frequent occurrence of conflicting findings and the numerous experiments with negative findings are disconcerting." (p 256).

measuring quadrant crossing in a small plastic box following a 72-h exposure to magnetic fields with the same parameters as in the passive avoidance study. Neither type of magnetic field affected the recorded activity.

Similarly, neither type of treatment affected pentylenetetrazol-induced seizure sensitivity studied in other mice immediately following a 72-h exposure. In that experiment, dosage for each strain of mouse was selected to produce a full clonic-tonic seizure in approximately 50% of the subjects within the 10-min observation period. That ensured the absence of a ceiling or floor effect.

Clarke and Justesen (1979) used a conditioned suppression procedure in a small study designed to see if a magnetic field could be detected by Leghorn chickens. The chickens, partially deprived of food, were trained to peck at a small disk. Pecks at the illuminated disk produced grain on a variable-ratio schedule. At irregularly spaced times a stimulus was presented for 90 s. Offset of the stimulus coincided with presentation of a 75-ms footshock. A reliable change in the response rate during presentation of the stimulus, in comparison to the rate during the immediately preceding 90-s period, was assumed to indicate that the subject could detect the stimulus. Four Leghorn chickens, 2 cocks and 2 hens, were studied under 3 stimulus conditions over 10 sessions each: 60 Hz, 1.7 mT (rms), DC 4.0 mT, and sham magnetic fields. Response rate did not increase or decrease reliably during the 90-s exposure periods. Mean average deviation in rate did increase reliably during exposure to either the AC or DC magnetic field in comparison to the sham exposure. Since the authors did not appear confident that the observed effects were the result of detecting the magnetic field we must share that concern. They expressed concern that unknown variables confounded with field presentation may have served as the controlling stimuli. If future experiments are to use a similar paradigm, it would be worth attempting to map the psychophysical function by varying magnetic flux density. In addition, the effect of the field itself on the baseline performance should be evaluated prior to pairing it with the shock since the reactions of the chickens, as described by the authors, could have been based directly on exposure to the field rather than on its pairing with the shock. That is, the field may have been eliciting reactions that directly affected the measured behavior, rather than serving as a discriminative stimulus, or a signal.

Smith and Justesen (1977) reported that exposure to a 60-Hz magnetic field

chance levels indicating that variables other than the field must have been controlling the high degree of accuracy seen earlier.

Davis et al. (1984) studied different behaviors of CD-1 male and LAF-1 female mice following exposure to a 1.5-T DC magnetic field for 72 h and LAF-1 female mice following exposure to a 60-Hz, 1.65-mT (rms) field for 72 h. A passive avoidance procedure was used to provide an index of memory. Immediately preceding exposure to the field each mouse was trained under the following procedure. It was placed into a start box, one of two compartments of the training chamber. A few seconds later the door between the compartments was raised. When the mouse entered the second compartment, it was exposed to electric shock, delivered via the grid floor, until it escaped back into the start box. Different groups of mice were exposed to different intensities of shock. The mouse was then removed from the chamber, and shortly thereafter either exposed to the magnetic field or housed in a control facility for 72 h. Immediately after the exposure period, the passive avoidance procedure was repeated but without the shock.

A common interpretation of this type of experimental arrangement is that "memory" is being studied. The datum of interest was the latency between raising the door between the compartments and entrance of the mouse into the shock compartment. If the latency to reenter the shock chamber following the initial treatment is greater for a rat exposed to shock than for one not exposed to shock, it indicates that the previous experience partially exerts control over that performance. If a second treatment--here magnetic field exposure--alters that retest performance, the effect frequently is attributed to a change in memory.

Issues related to the concept of "memory" are complicated and controversial (Hulse, Fowler, and Honig 1978). For present purposes we note that there were no differences in the dependent variable, i.e., latency to enter the second chamber, that could be attributed to exposure to the magnetic fields. A nice feature of the experimental design was the use of groups exposed to different shock intensities. Shock intensity was directly related to the latency to enter the second chamber during the retest in subjects not exposed to the magnetic field. Thus the failure to identify an effect of magnetic field exposure could not be attributed to a possible floor or ceiling effect produced by the value of the baseline itself.

Davis et al. (1984) also evaluated spontaneous locomotor activity by

mechanisms still are not well understood. Fourth, the fact that humans and rats appear to show an overlap in detection sensitivity, with the lower limit converging on approximately 1 to 2 kV/m, raises questions about scaling for equivalent exposures across species. If some effects of exposure--behavioral or others--depend on behavioral sensitivity, then behavioral equivalences will have to be determined for cross-species scaling; models based on average or peak field strengths, current densities, or other electrical parameters, by themselves, may not be sufficient. Fifth, under some conditions field exposure produces change in activity levels in rats and mice. Sixth, some evidence suggests that at higher field strengths the field can function as an aversive stimulus.

MAGNETIC FIELDS

A limited number of studies since 1977 have investigated potential behavioral effects of exposure to magnetic fields. Strong magnetic fields (>10 mT) produce visual sensations, called magnetophosphenes, in humans (e.g., Lovsund and Oberg 1979).

Tucker and Schmitt (1978) conducted a series of experiments designed to see if humans could detect 60-Hz magnetic fields. Subjects were asked to report presence versus absence of a field following each of 150 trials of 10-s duration. Fields were present for 50% of the trials. There was no evidence that the subjects could detect any of the fields that were studied. These included fields at 7.5 G (rms), 15 G (rms), 13 G (rms)/m, and 70 G (rms)/m. Attempts to establish detection of the field by providing feedback to subjects about the correctness of the response following each trial ("biofeedback," or learning condition) were not successful. A few subjects complained about headaches; however, the same subjects apparently complained about headaches during no-field exposures. The authors therefore concluded that the headaches might have been a result of exposure to the general experimental preparation rather than to the fields themselves. Although the conclusion is consistent with the observations, the data and the design are not sufficient for drawing any conclusion about the magnetic field's effect upon headaches. The report also describes the authors' attempts to eliminate possible artifacts or confounding variables. During earlier stages of their research, such factors were not obvious but some subjects were accurately reporting the presence of the field. Refinements in the exposure system, however, reduced accuracy to

produced in that strain of mice in the same environment where the exposure occurred; and that it could be measured by that laboratory. The electric field simply did not produce a sustained stress response. Corticosterone levels were also measured in mice exposed to the electric field for 2, 4, or 6 weeks; the levels did not differ from those of nonexposed controls.

Creim et al. (1984) reported that exposure to 60-Hz electric fields at 34, 69, or 133 kV/m failed to produce a taste-aversion reaction in male Sprague-Dawley rats. In this type of experiment, a distinctively flavored substance--one that the subject typically will eat or drink--is paired with an injection of an agent that produces a gastrointestinal disturbance or nausea. Consumption of the flavored substance is less likely when it is offered later. Consumption of a sodium saccharin solution, for example, is reduced if a rat was injected previously with lithium chloride following initial consumption. In the present experiment, rats were exposed to a 60-Hz electric field for 3 h following consumption of a 0.1% sodium saccharin solution. No differences in consumption were seen between groups following exposure or sham exposure. Injection of cyclophosphamide following consumption did produce the expected taste aversion, confirming the general adequacy of the test procedure. A tentative conclusion of ours is that aversiveness of a powerline frequency electric field is related to the magnitude of the peripheral stimulation produced by the field rather than to some kind of exposure-induced gastrointestinal distress. This conclusion is consistent with observations cited earlier that indicate that 60-Hz electric fields might be aversive at 133 kV/m. Garcia and Koelling (1966) showed that pairing peripheral, aversive electric shock with a saccharin drinking solution failed to reduce later consumption in comparison to the effect of pairing lithium chloride with the solution. Those results appear to be analogous to those reported by Creim.

Summary

When we survey the results of the detection, motor activity, and aversiveness procedures, we arrive at the following tentative summary with respect to exposure to powerline frequency electric fields. First, detection of the field occurs reliably within and across species. Second, threshold of detection may be stable for a subject, but it shows large variation among subjects within a species. Third, detection of the field seems to be based, at least partially, on peripheral stimulation produced by the field; however,

which they typically sleep. The swine did not spend more time out of the field during periods when swine are typically awake and active. It is interesting to note that the group of swine given the choice between the field and no-field had been exposed to a 30 kV/m, 60-Hz electric field in their home cage for approximately 3,400 h prior to the experiments. Furthermore, their shuttle activity apparently was greater than that of the nonexposed swine at the beginning of the experiment.

In the 23.5-h study, Hjeresen et al. (1980) also observed that rats spent more time in a 25 or 50 kV/m field than out of it during the period when the lights were on. When the lights were off they were more active. Other experiments are required to evaluate the generality of the phenomenon within and across species, as well as to evaluate its significance.

Apparently Sander, Brinkmann, and Kuhne (1982) also studied field aversion by rats. Although the rats apparently did not stay out of the field altogether, the report indicated that they slept out of the field and also spent more time out of it when active. Unfortunately the description of the experiment does not provide sufficient detail for an adequate evaluation, including the claim that the effect was observed down to 10 kV/m.

Although the results of the shuttlebox experiments indicate that under some conditions a powerline frequency electric field can function as an aversive stimulus, additional experiments are required to determine (measure or scale) the magnitude of aversiveness. We suspect that the field was not particularly aversive in those experiments. Moving <u>into</u> the field area occurred nearly as frequently for both exposed and nonexposed groups. Such an outcome would not be expected for an event if other techniques of measurement determined the event to be extremely aversive. Indeed, we wonder whether a field-induced increase in activity itself might explain, at least partially, the shorter latencies for leaving the field. A second factor to consider is that other indices of stress generally do not show changes for animals exposed to such high field strengths (Free et al. 1981). Although Hackman and Graves (1981) showed that circulating corticosterone levels of mice increased following 5 min of exposure to 25 or 50 kV/m, the levels quickly declined for exposures up to 2 h in duration. On the other hand, exposure to 100 dB-SPL noise produced an elevation of corticosterone that was sustained throughout a 2 h exposure to the noise. This positive control procedure demonstrated that a reaction often considered part of the nonspecific stress reaction could be

recognize that relationships between change in stimulus parameters and indices of aversiveness may be complex. Although stimulus parameters are fundamental, so too are the behavioral ones. Aversiveness is not a physical property of the stimulus; it is a behaviorally defined measure. The behavior depends jointly on stimulus, behavioral, and contextual parameters.

Determining the conditions under which a stimulus is aversive is of interest for several reasons. First, degree of aversiveness of a stimulus may be related to structural and functional indices of damage. Second, those same conditions may be sufficient to induce a nonspecific stress reaction. Third, since aversiveness is assessed by a change in behavior, a similar reaction--measured or not--could affect other behaviors of interest. A change in one behavior can alter other behaviors just as changes in other variables can. A careful behavioral analysis is required for adequately evaluating such possibilities. Fourth, a change in a measured behavior may affect exposure to the treatment variable itself even when the experimenter does not explicitly define that contingency. Thus, changes in posture or location in an electric field may alter the field characteristics and--under some conditions--thereby maintain those behaviors, as discussed under Motor Activity. Fifth, determining the aversiveness of exposure to EM fields may have practical significance with respect to nonhuman species. In particular, we may be concerned with the question of whether economically or ecologically valued species will escape from or avoid being exposed to such fields. Lee et al. (1982), for example, reviewed a small study that examined the location of cattle in relation to a prototype 1100 kV, 60-Hz transmission line that produced a maximum unperturbed field of 12 kV/m. The cattle ate and drank under the line, but spent "somewhat more time near the line when it was de-energized."

Hjeresen et al. (1980, 1982) demonstrated that under some conditions, rats and miniature swine would spend more time out of the field than in it. In the 45-min/session study, the rats spent more time out of the field at 90 and 105 kV/m but not at 0 (sham), 60, or 75 kV/m. In the 23.5-h/session study, the rats spent more time out of the field at 75 and 100 kV/m, with the greatest effect seen at the time of day when the lights were on--conditions typically associated with low levels of activity or sleep in rats. A similar 21-h/session study with miniature swine produced a similar outcome, i.e., the swine spent more time out of the 30 kV/m field during the conditions under

activity that could have masked a potentially similar reaction to exposure in the field. Third, the scheduled interexposure interval differed, one hour for Rosenberg and one week for Hjeresen. Fourth, the recorded activity was directly related to turning the field on and off in the shuttlebox experiments. In order to evaluate the possible role of the distribution and sequence of field onset and offset on activity per se, it would be necessary to expose subjects to those sequences independent of their behavior in the same chamber but with both halves being unshielded. Finally, mice were subjects in one study, rats in the other.

In a second experiment with rats, Hjeresen et al. (1980) studied shuttling behavior of individual rats during a single 23.5-h session. Mean shuttle responses were greatest in the first hour with the exposed groups (25, 50, 75, and 100 kV/m) responding even more than the nonexposed group. Mean number of shuttle responses were indistinguishable among groups after the first hour. However, interpretation of those results is complicated by the fact that the amount of time spent in the field was not equal across groups.

It is important to recognize that motor activity is a heterogeneous set of behaviors that can be broken into numerous classes. Different techniques of measuring activity may display different sensitivities to treatments (Robbins 1977). The force transducer studies and the shuttlebox studies do show that exposure to powerline frequency electric fields produces increases in motor activity of short duration. Does long term exposure affect activity? If it does, then the role of activity per se should be evaluated with respect to two other reported effects of exposure: (1) retarded repair of bone fracture (Marino et al. 1979; McClanahan and Phillips 1983), and (2) alteration of synaptic and neuromuscular function (Jaffe, Laszewski and Carr 1981; Jaffe et al. 1980). Field produced differences in activity also may play a role in some experiments designed to measure aversiveness of the field.

Assessing aversiveness of exposure to the field.

Operationally, a stimulus or condition is defined as being aversive if a subject will respond in order to reduce, eliminate, or prevent its occurrence. It is also aversive if the subject will respond less if responding increases exposure to the condition.

Stimulus parameters affecting aversiveness include intensity, duration, waveform, as well as temporal characteristics of stimuli presentation. We

reactions. The decrease in activity over repeated exposures to the field could be due to adaptation, habituation, or perhaps loss of novelty. A reduction in activity also might have occurred if, by assuming certain postures or staying in certain locations, effective field strengths were reduced. At least three reasons could account for the peak activity seen at 50 kV/m. First, it could have been an artifact of the dependent variable selected for analysis since the activity measure was a ratio based on baseline values. The comparison across field strengths assumes either that baseline values are equivalent (but data are not presented) or that they do not affect sensitivity to individual treatments (an untenable position). Second, higher field strengths might have produced "freezing", i.e., nonmovement following intense stimulation. Third, reduction in activity could have reduced either effective field strength or variation in field strength, both outcomes that might maintain low levels of activity.

Hjeresen et al. (1980) also observed increased activity in rats during exposure to 60-Hz electric fields in experiments designed to study aversiveness of the field as well. (See the next section.) The subjects could move between shielded and nonshielded halves of a shuttlebox. In one experiment, each rat was exposed to a 60-Hz field during a 45-min session once a week for four weeks. Shuttling between halves (Table 1, p. 310) occurred slightly more frequently for rats exposed to a field at 60 kV/m or greater than for rats never exposed to the field. The result persisted across sessions.

Although the Hjeresen et al. (1980) results seem to differ from those of Rosenberg et al. (1983), differences between procedures must be considered. First, their measures of activity were different. Rosenberg used force transducers that probably would have sensed jumping, walking, nosing, grooming, etc., whereas Hjeresen recorded shuttling movements (called "traverse activity" in the report), between halves of the shuttlebox. Second, in the Rosenberg study, subjects were placed into the chamber several hours prior to the first exposure, and they remained there across the repeated exposures. Increased activity produced by handling and novelty of the chamber, therefore, would most likely have been diminished by the time the initial baseline measures were recorded. In the Hjeresen studies, on the other hand, exposures apparently occurred shortly after handling and introduction to the chamber. Those factors could have produced increases in

conclusively; (2) the effect also occurs at strengths below the lower limit of detectability; or (3) the effect remains invariant while detectability is modified by some procedure.

Motor Activity

A frequently cited preliminary report by Moos (1964) indicated that exposure to 1 ±0.2 kV/m altered activity of male CFW mice. Several aspects of both the report and the experimental design appear to be inadequate for accepting the conclusion. (1) Field measurement techniques are not reported. We wonder whether magnetic switches, located under the plastic floor and used to monitor activity, significantly distorted the field. (2) Effective field strengths determined with mice or models in the cages are not reported. (3) Evidence is not provided to demonstrate the absence of microshocks occurring during eating or drinking. (4) Cages were not cleaned daily. It seems possible that local fields and electrical properties of the cages would have changed as the cages became dirty. In addition, the relation between cage cleaning, with the requisite handling of the mice, and field exposure is not clear since cage cleaning was not randomly related to field exposure. (5) The design of the experiment is not clear. It seems as if it were an AB design with all of the mice observed first under no-field and then under the field condition. If so, order of exposure was confounded with the number of days in the cage. The absence of a control or sham-exposed group precludes evaluating the significance of the order of observation.

Rosenberg and his coworkers (1981, 1983) reported that motor activity showed a transient increase under some conditions of exposure to 60-Hz electric fields. In those experiments, deer mice (Peromyscus leucopus) were housed individually in exposure chambers for several hours prior to exposure. One hour periods of exposure then alternated with one hour periods of nonexposure. Increases in motor activity occurred during the first hour, with the effect decreasing across successive periods of exposure. Rosenberg et al. (1983) reported that the minimum field strength required to produce the effect fell between 35 and 50 kV/m. Furthermore, the maximal percentage increase in activity over baseline values occurred at 50 kV/m, not at the higher field strengths studied, i.e., up to 100 kV/m.

The increase in activity could be based on elicited reflex reactions, on orientation-like responses to the field when it is detected, or on escape

strengths below the values reported by Cabanes and Gary (1981). Questions about mechanisms and attempts to scale across species may be thwarted if data are not obtained under functionally equivalent conditions.

Two additional factors need to be recognized when comparing detection experiments. Clothing was implicated as a variable influencing detection by humans. Distance from, or movement along, the surface of the plastic chamber has been suggested as a variable affecting detection by rats. Kaune (1981) showed that a 60-Hz electric field was enhanced at the surface of a physical model of a rat as it approached the wall of a polycarbonate plastic chamber.

Cooper et al. (1981) and Graves (1981) attempted to train three pigeons to detect 60-Hz electric fields using a conditioned suppression procedure (Smith 1970). Pecking an illuminated key was maintained by presenting grain on a variable interval, 90-s schedule. Equal numbers of field trials and control trials were presented randomly. Rate of responding during 15-s trials was compared to the immediately preceding 15-s period. A 60-Hz electric field was presented during field trials. Offset of those trials coincided with presentation of a 2.5 mA, 30-ms grid shock. In Experiment 1, with a 21 kV/m field in the region of the head, pigeons responded less during the trial than just prior to it; but in Experiment 2, at 10.5 kV/m, there was no difference. Since Cooper et al. (1981) indicated that "subjects seemed to suppress behavior during the few seconds following field onset rather than during the entire time the field was energized...", it is not clear that the suppression was the result of pairing the field with the grid shock or was a direct effect of exposure to the field.

We focus at length on detection of the electric field for several reasons. First, it is one effect of exposure that has been consistently demonstrated both within and across species, including humans. This may enable us to use nonhumans to investigate possible mechanisms. Second, attempts at scaling equivalent exposures across species make assumptions about mechanisms possible. Determining field parameters necessary to produce equivalent effects across species should help us identify whether peak or average field strength, peak or average current density, etc. serve as the controlling variables that one should equate for. Third, effects produced at strengths greater than that required for detection could depend primarily on detection occurring. That hypothesis remains tenable until one of the following conditions is met: (1) different mechanisms can be proven

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EFFECTS OF ELECTROMAGNETIC FIELDS ON CIRCADIAN RHYTHMS

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SUMMARY

Since Brown began to develop his exogenous clock hypothesis of how subtle geophysical variables could generate biological rhythms, chronobiologists have been interested in documenting how various types of electromagnetic radiation influence biological clocks (for a review of this debate, see Brown, Hastings, and Palmer 1970). Of particular interest have been the effects of electromagnetic fields on the circadian timing system. While life science research into effects of electric and magnetic fields is an area of some controversy, this report contends there is good evidence that electromagnetic fields can alter circadian rhythmicity. However, the lack of uniformity in experimental protocols, animal models, and exposure conditions has led to a variety of reported effects but no established test system which has been verified by different investigators. Consequently, it is difficult to assess the significance of these rhythm effects and their implications for public health.

INTRODUCTION

Diverse behavioral, physiological, and biochemical parameters are not constant in time but rather exhibit pronounced changes. Those variations which occur with a daily periodicity have been termed circadian rhythms. The word "circadian" has been used because--in the absence of temporal information from the environment--the natural (or free-running) period of such rhythms is normally only approximately 24 h. In nature, 24-h environmental cues serve to reset the "biological clocks" which time these rhythms so that the period is exactly 24.0 h, thereby permitting a constant phase relationship with solar time. This process is known as entrainment.

In addition to effects of environmental cycles on circadian entrainment, environmental conditions can alter the expression of circadian systems. Many

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factors can influence an observed rhythm without directly affecting the circadian pacemakers which time the rhythms. Such responses are referred to as masking. Light and dark are known to be powerful masking agents, and their masking effects often obscure circadian rhythm data and confound analysis. For example, in nocturnal rodents light during the night inhibits the activity and darkness during the day can stimulate activity. To fully assess the circadian effectiveness of agents which also cause masking, it is necessary to have experimental paradigms which minimize masking responses.

The circadian timing system is one of the more remarkable biological regulatory processes in the body. This system serves to organize various behavioral, physiological, and biochemical events so that they are externally synchronized with the environment and internally synchronized with other bodily functions. The temporal organization insures that specific functions have the proper phase relationships. For example, there is a rhythm in the secretion of digestive enzymes. It is clearly better for this rhythm to be high during the portion of the 24-h day when the feeding rhythm is high than when the feeding rhythm is low. The adaptive value of the circadian timing system is evident from its ubiquity in nature and it has been described in all major classes of animals.

Although there is still a great deal to be learned about the anatomy and physiology of the circadian timing system, some aspects of its structure and function are understood. The system is thought to consist of several logically distinct elements: transducers, which sense temporal cues from the environment; pacemakers, which provide the endogenous 24-h timekeeping functions; mediators, which are neural or hormonal pathways that transmit temporal information from the pacemakers to other physiological systems in the body; secondary oscillators, which are physiological systems capable of inherent rhythmicity but normally are under control of the circadian pacemakers; passive elements, that is, physiological systems involved in the generation of rhythms but not capable of endogenous rhythmicity; and overt rhythms, those parameters which are actually measured and exhibit regular oscillations with circadian periods. All of these elements of the multioscillator system are normally coupled together and operate in synchrony.

To evaluate the function of the circadian timing system it is necessary to simultaneously monitor several elements of the system. This is usually done by following several circadian rhythms of subjects in various experimental

conditions (e.g., Aschoff 1965; Sulzman, Fuller, and Moore-Ede 1977, 1979). One of the common features of the timing system is the fact that the endogenous pacemakers have a natural period that is different from 24.0 h. Thus, in order for these rhythmic processes to remain synchronized to the solar day, temporal cues from the environment must reset these biological clocks each day. The circadian timing system is sensitive to different types of environmental stimuli including light, temperature, sound, food availability, and electromagnetic fields. Normally these factors present coherent temporal patterns, i.e., environmental temperature is usually high during the day and low at night. However, conflicting environmental time cues can force internal desynchronization of rhythms (Sulzman et al. 1978). In this condition, separate rhythmic variables of an individual show different period lengths. The breakdown in the internal order can result in both physiological and behavioral deficits. Because of the sensitivity of the circadian timing system to the environment, it is possible that the electromagnetic fields may effect the phase relationships and coupling of the various elements of the circadian timing system.

The proper functioning of the circadian timing system is important for human health. There are prominent daily variations in most physiological systems of the body, as well as behavioral performance levels, sensitivity to drugs and toxins, and many other parameters (Moore-Ede, Sulzman, and Fuller 1982). Disruptions in the circadian system can result in disturbances to the sleep-wake cycle (Kokkoris et al. 1978). Additionally, alterations in circadian rhythms are associated with psychiatric illness (Wehr et al. 1979) and performance (Klein and Wegmann 1979).

There is also evidence that disorders in circadian rhythmicity can produce physiological deficits in nonhuman primates (Fuller, Sulzman, and Moore-Ede 1978a, 1978b). These authors have shown that squirrel monkeys in constant environmental conditions are frequently unable to thermoregulate properly. If exposed to a mild cold pulse (6 h of 20°C) monkeys often cannot maintain core body temperature if the circadian timing system is not functioning properly. If electromagnetic fields do alter the normal functioning of the circadian timing system then internal conflicts in body time may result from changes in pacemaker activity or alterations in mediator function. As has just been described, such perturbations in the circadian timing system can influence physiological function.

LITERATURE REVIEW

It had been long suspected that electromagnetic fields affect circadian rhythms. For many years Brown (1970) postulated an exogenous origin of circadian rhythmicity. He contended that subtle geophysical variables (e.g., electromagnetic fields) were an intrinsic part of nature and played an important role in providing time of day information to organisms. Brown and his students were among the first to demonstrate that various types of geophysical signals could be sensed by biological systems.

(1). Probably the most significant work on the effects of electromagnetic fields on circadian rhythms was conducted by Wever (1971, 1979). In Aschoff's Max Planck Institute at Erling Andechs, West Germany, Wever used two underground rooms that were built so that humans living in either room had no indication of solar time. There were no windows, TV, radio, clocks, etc. This temporal isolation facility was used for about 20 years and pioneering work was done on the characteristics of the human circadian timing system. For the several years the rooms were identical except that one was lined with several layers of jointless steel plate casing. This room was effectively shielded from the earth's electric and magnetic fields; no radio signals could be detected and compass direction could not be determined in the shielded room. However, there were weak 50-Hz AC fields induced by electric wiring in the room for lights and other electrical appliances.

When comparing the results of subjects in the shielded and unshielded rooms, he noted that there was a slight increase in the average free-running period of subjects in the shielded room (25.11 h) compared to the unshielded room (24.85 h), ($p < 0.05$). Wever also observed an almost threefold increase in the incidence of spontaneous internal desynchronization in the unshielded room (35 vs. 12, $p < 0.05$). The shielded room was equipped so that artificial fields could be generated. Wever first examined the effects of DC fields, first electric (300 V/m) and then magnetic (1.5 G). Neither of the fields affected the free-running period or the incidence of internal desynchronization.

When subjects were exposed to certain AC fields different results were observed. With 10-Hz square wave electric fields (2.5 V/m), Wever found that the free-running period was reduced. In these studies subjects served as their own controls, and so for part of the experiment the subject was in the shielded room with no 10-Hz fields, and then for the remainder of the

experiment the subjects were exposed to 10-Hz fields. In the control portion of these experiments, the free-running period was 26.22 h, while in the 10-Hz field portion the period was 25.01 h ($p < 0.01$). Wever also showed that there was a marked decrease in the incidence of initial desynchronization in the 10-Hz fields. None of the 17 subjects showed internal desynchronization as long as the 10-Hz fields were in continuous operation.

The free-running rhythms of humans could be entrained by 24-h cycles in which the 10-Hz fields were on for 12 h and then off for 12 h. This is an important confirmation that 10-Hz fields affect the human circadian timing system. An additional important observation of Wever was that 10-Hz AC fields (2.5 V/m) imposed as sine waves did not produce the same effects as the square wave fields. This suggests that perhaps harmonics in the 10-Hz square wave fields produced the circadian rhythm effects.

In general, the quality of Wever's work is high. Aschoff and he pioneered the work on elaborating the multioscillator nature of the human circadian timekeeping system. Further, Wever was trained as a physicist and consequently has an excellent theoretical appreciation of the physics of field exposure. Unfortunately, the retirement of Aschoff means that this unique facility will no longer be used for electromagnetic field studies.

(2). In 1969, Dowse and Palmer reported that the circadian rhythm of wheel running activity could be entrained by electric fields. They reported that about 50 of the mice (Mus musculus) in a 500 V DC field, on for 12 h and then off for 12 h, showed a 24-h period. However, 3 of the 6 mice that showed a 24-h period had their activity during the fields-on period, and the other 3 were active during fields-off period. This bi-stability of phase angle is quite unusual.

The work of Dowse and Palmer has been criticized on both technical and theoretical grounds by Roberts (1969). He argued that noise from the field generating equipment and corona discharges could have resulted in artifacts (see the above description of masking). Further, Roberts contended that the energy levels were several orders of magnitude too small to produce biological effects because of skin insulation.

(3). Bennett and Huguenin (1969) studied the reaction times of earthworms (Lumbricus terrestris) at two different times of day, 1200 and 2000 EST, for 63 days. Some worms were kept in a Helmholtz coil producing a magnetic field opposite to that of the earth so that the net field was approximately zero.

Other worms were kept in the earth's field. The time for these latter control worms to exhibit a light withdrawal response was 7.2 s at 2000 and 8.9 s at 1200. Worms that were kept in the coil showed identical response times (8.8 s at 2000 and 8.7 s at 1200). Since the magnetic field of the earth varies during the day (approximately 0.6 G at 2100 and about 0.3 G at 1500 (Stutz 1971)), Bennett and Huguenin proposed that the natural daily geomagnetic field variation was the cause of the response time difference at the two times, and that when the daily geomagnetic field was cancelled, no difference was seen.

These results are interesting, and suggest that the earth's geomagnetic field alters neural processing of the light avoidance response of earthworms. However, from a circadian rhythm standpoint the experiment is difficult to interpret. The paper suggests that the worms were kept in constant darkness except while being tested. No other monitor of circadian rhythmicity was followed so it is difficult to assess the status of the circadian timing system of these animals. Further, since only two times were examined and no raw data were presented by the authors, it is not possible to critically evaluate this study.

(4). Bitz and Sargent (1974) examined the effects of magnetic fields on the circadian rhythm of conidiation (asexual spore formation) of the common fungus, Neurospora crassa. In a thorough series of experiments, they measured the rhythm under three test conditions: constant fields, cyclic fields on for 12 h and then off for 12 h, and pulse fields which were on for 20 min every 24 h. Magnetic field intensities of 6 and 32 G were examined. No effects on the period of the rhythm or the growth rate of the cultures were seen in any of the test conditions.

These results are quite important because they represent one of the few well controlled studies of effects of fields on a microbial circadian system. Extensive studies of the genetics (e.g. Feldman 1983), biochemistry (e.g. Roeder, Sargent, and Brody 1982) and physiology (e.g. Francis and Sargent 1979) of the Neurospora circadian clock have been conducted. They have shown that this lower organism has many of the same clock characteristics (light effects, chemical sensitivity and temperature responses) that higher organisms exhibit. The results of Bitz and Sargent may indicate that magnetic fields may only affect organisms with a nervous system. It is unfortunate that these studies did not examine effects of AC electromagnetic fields.

(5). Halberg and coworkers (1975) have conducted a series of

investigations utilizing a variety of test organisms and field conditions: 45 to 75 Hz, 0.4 to 2 G, and 1 to 180 V/m, with various duration exposures. They reported that there were no reproducible effects on circadian rhythms of the movement of silk tree leaflets; insecticide susceptibility of flower beetles; susceptibility of mice to ouabain injections; or on mice body temperature, food consumption, estrous or survival rate. However, their experimental design was such that they could not examine the same effects that were reported by Wever (1971). First, all of their measurements were done on organisms whose circadian rhythms were entrained, not free-running as in the Wever studies. Second, masking by the light-dark cycles may have obscured small effects of these fields. Third, these experiments followed only one rhythm at a time, so that internal dissociation or desynchronization could not be observed.

(6). Dowse (1982) studied whether cycles (12-h on and 12-h off) of 10-Hz electric fields (150 V/m) affected the locomotor rhythm of individual fruit flies (Drosophila melanogaster). He concluded that the cycle of the 10-Hz fields could synchronize the rhythm to a period of 24 h, and that when the field cycle was advanced by 6 h, the activity rhythm began to shift towards the new phase.

There is little control data presented in the paper; and the control data that Dowse does show, suggest that the value of the free running period may depend on which days are used in the calculation. That is, the period may be close to 24 h at the beginning of constant conditions and then change. It is not possible to determine the level of individual variability in this study, and if it is as large as the data indicate, then Dowse's use of short-time series (5 days) to calculate the period is probably not sufficient. These data are interesting but not convincing.

(7). A clear but surprising effect of 60-Hz electric fields was shown by Wilson et al. (1981). After 30 days of exposure, rat pineal function was examined by monitoring the circadian patterns of 5-methoxytryptophol, melatonin, and serotonin-N-acetyl transferase. The latter two compounds typically show nighttime levels that are severalfold higher than daytime levels. Field exposure depressed the melatonin rhythm and also reduced the rhythm of serotonin-N-acetyl transferase activity. The nighttime levels of 5-methoxytryptophol were higher in exposed rats than in controls, suggesting that an alternate pathway of tryptophan metabolism is activated by the field

exposure. The most surprising aspect of this study is that a transformer malfunction reduced the field strength from the desired 65 kV/m to 1.7 to 1.9 kV/m. These exposure levels are very low, and thus the effects on pineal function are quite remarkable.

(8). Over the last several years Ehret and coworkers (1979, 1981) have developed a facility to produce highly uniform and homogeneous electromagnetic fields for rodent circadian rhythm studies. Two types of animals, rats and mice, have been used in this work. Rats (2 to 7 months of age) have been exposed to 60 Hz, 4.5 to 55 kV/m fields in a variety of experimental paradigms including: continuous fields in light-dark with feeding schedules or constant darkness and food deprivation; intermittent fields (12-h on and 12- or 13-h off) with constant darkness and food deprivation; and high frequency intermittent fields (e.g. 1-min on and 1-min off). In these studies, core body temperature, activity, and body weight were monitored. These experimental conditions produced no effects on rat circadian rhythms.

The significance of these rat data is difficult to assess because of the feeding schedules that were used. Ehret and coworkers routinely used feeding cycles or complete food deprivation in their rat studies, and they may be the only group that relies on this paradigm. A major criticism of this protocol is that the DDSS (constant darkness with complete food deprivation) assay of the free-running period limits the duration of the experiment to about 6 days, and it is often difficult to finely resolve time series of this length. Also, the data obtained are from starving and therefore highly stressed animals--hardly an optimum animal model.

In the mice studies, Duffy and Ehret (1982) reported that the activity and gas metabolism rhythms of male mice (Peromyscus leucopus) could be phase shifted by exposure to vertical AC electric fields. Mice who were free-running in constant darkness were pulsed for 0.5 h of 100 to 130 kV/m, and then given 0.5 h of ambient fields, then 0.5 h of 100 to 130 kV/m, and then ambient fields for the remainder of the experiment. When the intermittent pulse occurred during the early active phase, a phase delay of activity and metabolism resulted. Pulses during the early inactive phase produced a slight phase advance of both rhythms. These latter pulses also induced splitting, a situation in which the normally consolidated activity pattern splits into two distinct components which usually then free-run 180° out of phase. Unfortunately, at the present time, data from this facility has

ly been published in abstract form and consequently these results cannot be lly evaluated.

These results are important because--if responses to field exposure depend the time of the circadian cycle--this indicates that these exposures are ting on circadian pacemakers, the SCN (suprachiasmatic nuclei in the othalamus). Further, since there is evidence that splitting is caused by coupling of the bilateral SCN, the observation of splitting induced by field osure further supports the notion that circadian pacemakers are affected.

Duffy and Ehret (1982) also reported that 9-h exposures during the active ase (subjective night) caused phase delays and induced torpor. litionally, they tested a nude strain of hairless mice and showed that field osure produced the same arousal response during the inactive phase as was en in wild type mice.

(9). Recently Sulzman and Murrish have begun examining the effects of ectromagnetic fields on the circadian timing system of squirrel monkeys aimiri sciureus). As part of the New York State Powerline Project an ectromagnetic field exposure facility has been designed, constructed at the ate University of New York at Binghamton, and certified by the National reau of Standards. This facility is currently being used to test the fects of 39 kV/m, 1 G; 26 kV/m, 1 G; and 2.6 kV/m, 1 G exposure levels on e feeding and metabolism rhythms of monkeys free-running in constant light. ere are preliminary indications that electromagnetic fields may alter the ee-running rhythm of squirrel monkeys (Sulzman, Murrish, and Sickles 1984). is study is the only current investigation of electromagnetic field effects primate circadian rhythms.

The use of monkeys rather than rodents as human surrogates in research on ectromagnetic field effects is important because there are differences tween rodent and primate circadian physiology. First, the evidence for the ltioscillator nature of the circadian system is not as well established in dents as in primates because internal desynchronization of circadian rhythms s not been documented in rodents. Second, there are key differences between e way in which rodents and primates respond to environmental temporal cues ulzman, Fuller, and Moore-Ede 1979). Third, electromagnetic fields produce fferent body currents in 2-legged animals (primates) with a vertical ture, than in 4-legged animals (rodents) (Bridges and Preache 1981). Thus, order to fully assess the importance of Wever's observations, the effects

ırmonal (estrogen) and neural (light/dark) stimuli influence the electrical tivity of the suprachiasmatic nucleus (Pardey-Borrero, Tamasy, and Timiras ı85); similarly, increased circulating levels of corticosteroid hormones may .imulate neuronal excitability and metabolism (Woodbury, Timiras, and ·rnadakis 1957); and alterations (fluidity, receptors) in the cell membrane y alter the binding and transport of hormones (e.g., thyroid hormones) in ıe cell and, thereby, change cellular responsiveness to environmental cues. ·vertheless, even desynchronization of neuroendocrine regulators may be ısufficient to disrupt biologic clocks in the majority of individuals with ımpetent homeostatic adjustments. However, in some special cases (e.g., ıdividuals with special working shifts, individuals with rhythm disorders), 'en a minimal degree of desynchronization may exacerbate the instability of ıeir cyclic activities. In these individuals, other factors, in conjunction th ELF fields, may combine to aggravate their condition.

The critical role of the neuroendocrine functions in regulating the major 'ents of growth and development from fertilization, to birth, to adolescence , well documented by clinical and experimental studies. More recently, this 'stem has also been implicated in regulating the process of aging (Meites ı83). In fact, the entire life span has been viewed as a cycle of events 'iven by neural and endocrine signals programmed to insure the passage from ıe stage of life to the next, terminating in death. Thus, aging and death ıy be programmed through specific neuroendocrine signals or may result from ıilure to adapt to the environment (Timiras 1978; Timiras, Choy, and Hudson ı82; Walker and Timiras 1982). In the first case, environmental factors such ELF fields may influence the program by inducing chromosomal damage and ıtations (as claimed, but with little evidence); in the latter case, they may ıd to the burden of environmental insults (e.g., the stressor hypothesis). either case, the role of ELF fields in the aging process, the length of the fe span, and the etiopathology of disease (pathology increases as the ıdividual ages) should represent an area of study to be pursued vigorously. ıile some attention has been given to the special effects of ELF fields in ıildren (e.g., with respect to incidence of leukemia) and to growth and ·velopment (e.g., growth rate, incidence of congenital malformations) bernett [illegible]; [illegible]avitz 198[illegible]) none has been dedicated to possible influences on [illegible] and in the middle-aged (often the age of the exposed [illegible] populations.

natural hazards, is still unknown but appears, so far, minor. Nevertheless, some investigators have suggested that the ELF fields may act as stressors, and as such, severely challenge homeostatic competence (Anderson 1985; see Marino this publication).

However, evidence for such an effect is still lacking. The classical view is that stress activates the hypothalamo-sympathetic-pituitary-adrenocortical axis, therefore, in order to demonstrate that a certain environmental change acts as a stressor, a systematic study at all levels of stimulation of this axis is in order. Yet the only reports available are concerned with circulating corticosteroid levels, and even these are contradictory, some studies showing a decrease in the hormones after exposure and others an increase. Similarly the response to a second simultaneous stress shows contrasting results with some authors reporting a delay in fracture healing in exposed rats as compared to controls and others no difference in the response to cold in control and experimental animals (Hilton et al. 1978; Marino et al. 1977, 1979). Thus, the possibility that ELF fields act as a stressor--while perhaps an attractive hypothesis--has so far no clinical or experimental support. That ELF fields may affect some types of biologic cyclicity, such as circadian rhythms, is a subject of extensive study and one of relevance to neuroendocrinology (see Sulzman this publication). Circadian rhythms (so-called because, in the absence of environmental cues, the natural, free-running period of the rhythms is "circa," i.e., approximately, but not exactly, the length of the day "dies," i.e., 24 h) drive several important body functions (e.g., sleep-wakefulness, endocrine functions, digestive enzyme secretions, motor activity). Regulatory centers for these rhythms have been localized at various levels. At the periphery, sensory transducers are responsive to environmental cues (e.g., light/dark of day) and send the information to central pacemakers situated in the brain providing the timing for the rhythm. One such pacemaker has been identified in the suprachiasmatic nucleus of the hypothalamus and has been shown to be sensitive to both neural (e.g., light/dark) and hormonal (e.g., estrogen levels) stimuli. From these pacemakers, neural and hormonal signals transmit the information from the pacemakers to the target tissues. The complexity of the neural and hormonal relationships to the environment makes it possible to envision that even minor alterations simultaneously affecting several elements of the neuroendocrine system may result in significant shifts of the biologic rhythms. Indeed,

Ca efflux may be increased in neuronal cells upon ELF fields exposure, in B pancreatic cells, Ca^{++}, efflux appears decreased and, simultaneously, insulin release is also reduced. Although these observations seem to be opposite of those reported for neurons where Ca^{++} is increased, they point to a possible selectivity of ELF fields for the membrane, as those other studies did.

The pineal, a putative endocrine gland, has been investigated for its relationship to the light/dark daily cycles and its secretion of melatonin, a postulated antigonadal hormone (Anderson 1983, 1985; Anderson et al. 1982; Cremer-Bartels, Krause, and Kuchle 1983; Wilson et al. 1980, 1981; Zatz and Weinstock 1978). In rats exposed to ELF fields, levels of melatonin in the pineal are generally reduced, particularly during the night when the nocturnal peak is depressed. It has been suggested that this observed decrease in melatonin depends on decreased availability of its precursor, serotonin (Wilson et al. 1981). Inasmuch as serotonin is an important and widely-distributed neurotransmitter in the brain, reduced levels of melatonin may be important for their relation to cyclic functions, including reproduction, as well as an indirect manifestation of neurotransmitter deficits under exposure to ELF fields.

HOMEOSTASIS, STRESS, AND BIOLOGIC RHYTHMS

Survival of the individual depends on the capacity to maintain homeostasis, i.e., the constancy of the internal milieu in response to the demands of a changing environment. The impact of any change in the environment can be best judged by the magnitude of the adjustments the organism is required to make to maintain homeostasis. When these adjustments are adequate, adaptation is successful and survival ensues; when they are not, the results are maladaptation, disease, and, ultimately, death. An overview of all the described effects of ELF fields indicates that the demands--if any--these fields impose on the organism are moderate; physiologic adjustments, for the most part, are adequate; and pathologic consequences are rare. However, it cannot be excluded that they may represent a potential danger for the well-being and survival of humans and other living organisms when one considers that these fields are superimposed upon the multitude of environmental demands to which living organisms are continuously exposed. The weight of this potential danger, as compared to the myriad of manmade and

significantly reduced uptake of T4, suggesting the occurrence of extrathyroidal hypothyroidism (Udintsev, Serebrov, and Tsyrov 1978). With respect to the parathyroid hormone (also secreted by the thyroid gland), in vitro studies suggest that the well-demonstrated effects of ELF fields on bone healing may be due to an inhibition of parathyroid hormone secretion, or, perhaps more likely, to the blocking of the osteolytic effects of the hormone at the bone tissue level (Luben and Cain 1982). With respect to the thyroid hormones, this is again an indication of changed (decreased) responsiveness of the target tissue to the hormone. Studies of hormone receptors, hormone binding, and intracellular metabolism are clearly in order, but none has been published so far.

In view of the hypothesis that ELF fields may act as stressors (see below), the adrenocortical function has been the subject of several studies, most of them limited to measurement of the circulating hormones. In general, corticosterone levels were increased in exposed rats, probably in response to increased adrenocorticotropic (ACTH) stimulation. This increase occurred also in adrenal slices incubated in vitro and exposed to ELF fields, and suggests a direct action on adrenocortical tissue; furthermore, in these in vitro studies, the increase in corticosterone secretion followed only certain exposures revealing a field intensity "window" for corticoid responses (Lymangrover, Hsieh, and Dunlap 1983; Lymangrover, Keku, and Seto 1983). Additional studies in rats, in which sequential blood sampling could be obtained through chronic indwelling carotid cannulae, showed the abolition of the characteristic circadian peak of corticosterone, suggesting alterations not only in hormone levels occurring at the adrenal gland level, but also disturbances of the secretory rhythm probably involving hypothalamic centers (Lu, Michaelson, and Pettit 1982; Michaelson et al. 1982; Quinlan et al. 1983). These studies also showed, by the use of pharmacologic agonists and antagonists, that increased secretion of corticosterone could be induced not only by increased levels of ACTH but also by stimulation from other brain peptides, i.e., endorphin, and neurotransmitters, i.e., norepinephrine.

Studies of the endocrine function of the pancreas have centered exclusively on insulin and have focused on the relationship (still little known) between Ca^{++} movements and hormone release. One hypothesis is that Ca triggers the movement of contractile proteins in the microtubular system and thereby stimulates exocytosis and secretion (Jolley et al. 1983). While

time of day). In view of these considerations, it becomes extremely difficult to obtain a reliable endocrine profile in humans exposed to ELF fields, and, indeed, none is available at present. Even with experimental animals, the studies which have been so far reported are extremely fragmentary and incomplete and confined almost exclusively to reporting changes in circulating hormone levels.

Studies on hypothalamic-hypophysiotropic (releasing and inhibiting) hormones have not been conducted, to my knowledge. With respect to the hormones from the paraventricular and supraoptic nuclei, the decapeptides oxytocin, and the vasopressin (or antidiuretic hormone, ADH), the few studies available have reported increased circulating levels of ADH in rats after exposure to ELF fields. This may be a direct hypothalamic stimulation, although hypothalamic levels of the hormone were not measured. As a consequence, diuresis was diminished (Carmaciu, Groza, and Danelius 1977). At the level of the anterior pituitary gland, no changes or only slight decreases of tropic hormones have been reported, as demonstrated by normal or moderately and transiently reduced levels of prolactin, growth hormone, thyrotropin, and gonadotropins (Chernoff 1985; Free et al. 1981; Margonato and Viola 1982; Michaelson and Quinlan 1982; Phillips 1983a, 1983b; Quinlan et al. 1980, 1983; Sasser 1983; see Sikov this publication). Accordingly, studies in miniature swine and guinea pigs and preliminary studies in rhesus monkeys did not show any deficits in fetal and postnatal growth as well as breeding performance and fertility in the generations born and raised with ELF fields. Conversely, other studies in mice and rats report decreased testicular weights, stunted growth, and increased incidence of congenital malformations under similar conditions of exposure. Yet, one of the studies in rhesus monkeys reports greater body weight gain in the exposed animals than in controls, but only in the males and not in the females. This may be related to a stimulatory endocrine (testicular) action (Grissett 1979).

Because of the role of thyroid hormones in growth and metabolism, several studies measured blood levels of thyrotropin (TSH) and thyroid hormones (T3 and T4), primarily in rodents, without observing any significant change in animals exposed to ELF fields (Lafreniere and Persinger 1979; Lu, Lebda, and Pettit 1981; Lu, Michaelson, and Pettit 1982; Lu et al. 1982); Persinger, Lafreniere, and Carrey 1978). However, one report indicates that, while the circulating levels of these hormones remain normal, the target tissues show a

disturbances could be translated in sympathetic-endocrine activation leading to neurotransmitter (e.g., decreased tyrosine hydroxylase activity in the hypothalamus and brainstem) and hormonal (e.g., increased corticosterone secretion) imbalances manifested as stress responses, disruption of thermoregulation, and alterations in water consumption and reproduction (Boulant and Demieville 1977; Fam 1980; Rosenberg, Duffy, and Sacher 1981; see Marino, Sikov this publication).

Studies on the mechanism of ELF field action focus on the role of Ca^{++} shifts. Increased Ca^{++} efflux under the influence of these fields would be associated with Ca-dependent cellular processes, in particular neurotransmitter release and synaptic transmission. If such Ca^{++} changes reported in neurons were also to occur in endocrine cells, they could be responsible for eventual changes in the release of hormones. However, some of the experiments reporting increased Ca^{++} efflux have been criticized on methodological grounds, and the only acceptable evidence is that utilizing synaptosomes and neuroblastoma cells (see Albert and Slaby this publication). While Ca-efflux studies are extremely popular today--however controversial in this case--they depend in part on membrane permeability. With this in mind, it would seem that membrane changes may occur at any level of the neuroendocrine-target tissue axis, although little information is currently available on this aspect. Membrane changes should be considered in terms of structure and fluidity as well as of plasma and intracellular membranes and might affect the sensitivity of the cell to ELF fields, as well as modify its ability to respond optimally to neuroendocrine signals.

EFFECTS ON THE ENDOCRINE SYSTEM

The study of the changes which may occur upon exposure to ELF fields (as well as to a variety of other environmental factors) presents considerable difficulties that are related to many variables, depending on the nature of the endocrine function which is, itself, responsive to many environmental stimuli. Among these variables, some are related to genetic status, sex, and race differences; physical status; degree of exercise and hygienic habits (e.g., smoking, drugs); socioeconomic status; etc. Other factors depend on the methods of measurement, for example, the type of diagnostic test (e.g., secretory activity, hormone levels in plasma, free versus conjugated hormones, hormone metabolism, transport and receptors), and the time of testing (e.g.,

EFFECTS ON THE CENTRAL NERVOUS SYSTEM

The effects of ELF electromagnetic fields (EMF) on several aspects of nervous system structure, function, and behavior have been reported in several publications, and the major results evaluated recently specifically (Anderson 1985; see Albert and Cohen, Albert and Slaby, Stern and Laties, Wachtel, Wolpaw et al. this publication) or generally (Becker 1984; see Carstensen, Marino, Winters and Phillips this publication). Human studies conducted in various countries did not reveal consistent neurologic or psychologic changes in populations exposed to ELF fields and the reported symptoms (e.g., headache, irritability, fatigue) could be ascribed to any of the many variables to which the populations were exposed (Savitz 1985). Experimental work has employed a variety of models ranging from mammals (monkeys, cats, rabbits, swine, rodents, chicks) to Aplysia, brain slices, and cultured neuroblastoma cells.

The list of reported effects includes: alterations in spontaneous (e.g., EEG) and evoked (e.g., in retina, hippocampal slices) electrical activity; visual stimulation (e.g., phosphenes); increased synaptic excitability and alterations in neurotransmitters; altered neuronal structure (e.g., in Purkinje, hippocampus, and amygdala cells); gliosis; increased arousal and sleep disturbances; altered brain metabolism and vascularization; and behavioral disturbances involving specific senses (e.g., taste, olfaction) and specific or general tasks (e.g., avoidance, preference/aversion) (Anderson 1985; see Stern and Laties, Wolpaw et al. this publication).

Only a few studies have dealt directly with the hypothalamus. Some of these have raised a number of worthwhile questions, such as whether EMFs may have a selective action on different brain structures. In the list of neurophysiological effects of EMF listed above, the choice of the nervous structure or cell to be studied was based primarily on the availability of suitable techniques and the preference and expertise of the investigator. When asked whether EMFs had regional brain specificity, the reticular formation (RF) appeared to be the most sensitive (according to some investigators it was the cerebral cortex), followed by the hypothalamus (Kashtanov and Sudakov 1981). Disturbances of the relationship between the RF and the hypothalamus, as well as between the hypothalamus and the limbic system, another brain region sensitive to EMF, could be ascribed to EMF effects (Kashtanov and Sudakov 1981). Such reticulo-limbic-hypothalamic

centers to the target tissues and vice versa. Thus, some of the effects ascribed to ELF fields, as may occur in humans occupationally exposed to these fields, may be better analysed in terms of disruption of neuroendocrine regulation than--as usually are--in terms of specific modalities (see Michaelson this publication). For example, reduced sexual potency is not a matter exclusively of gonadal dysfunction but of impairment of the limbic-hypothalamic-pituitary-gonadal axis. Likewise, greater variability of pulse and blood pressure, loss of appetite and nausea may be viewed as resulting from alterations in hypothalamo-sympathetic- endocrine control; irritability, headaches, and increased nervousness may be the consequences of increased brain excitability, perhaps subsequent to endocrine alterations.

Therefore, one of the tasks of this report is not only to review the meager available information, but also to point out its inadequacy and to present a plea for more extensive studies in this vital area. Effects of ELF fields on the nervous system have been the subject of several studies and reviews, and these data will be referred to briefly here. Few studies have been conducted on the neuroendocrine cells of the hypothalamus, and, of those, some are related to alterations in ADH actions. Further investigations are sorely needed in this area. Also, few studies have examined effects on pituitary function.

The peripheral endocrines, their actions on metabolism, adaptation, and rhythmic activities, will represent the major portion of this review. Little is known about the effects of ELF currents on the responsiveness of target tissues to neuroendocrine signals (e.g., receptors for neurotransmitters and hormones, cellular transport, and metabolism, except, perhaps, increased Ca^{++} efflux in neural cells), and the sparseness of the data urges for more studies on this subject.

In view of the above considerations, demonstration of positive effects of ELF fields at one specific level (organ, cell, and molecule) may have little implication for the overall competence of selected functions or for human and animal health and survival. It is, thus, appropriate to ask that, in the absence of sufficient, systematic, and vigorous studies, concern about biomedical effects of ELF radiations be directed to increasing our understanding of these effects and not to discontinuing ELF fields utilization and study.

EFFECTS OF ELF ELECTROMAGNETIC FIELDS ON NEUROENDOCRINE SYSTEMS

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INTRODUCTION

The neuroendocrine system includes both the central nervous system and the endocrine system. Together, these two systems regulate body functions through a structural and biochemical hierarchy involving several levels of integration. The central nervous system, particularly the hormone-secreting (neurosecretory) cells of the hypothalamus, regulates the pituitary gland which, by its secretion of the tropic hormones, regulates the peripheral endocrine glands. These, in turn, produce and release the active hormones which act on the target cells (including neural cells) to carry out the signals initiated by the hormones. Communication among the components of the system is maintained by positive and negative feedbacks and is orchestrated by pacemakers which provide control for the rhythmicity of several neuroendocrine functions. The effective coordination of the components of the system ensures survival of the individual and of the species. Survival of the individual is assured by homeostatic adjustments for adaptation to the environment; survival of the species is assured by control of reproductive function.

Because of the key role of neuroendocrine functions in adaptation, any change in the environment, including those induced by extremely low frequency (ELF) currents, should be reflected in neural and hormonal alterations. Similarly, any intervention to restrict deleterious effects would be most efficacious in this system. Despite the physiologic importance of this system, the study of the effects of ELF fields thereon has so far been neglected and, in evaluating the few available investigations, one must be concerned not only with the many variables involved (related to the characteristics of the exposure, the biological variables, and the multifactorial epidemiology) but also to the characteristics of the system itself. Indeed, one of these characteristics is its kaleidoscopic nature that requires a proper integration and propagation of signals from the higher

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rhythms within individuals. Until enough investigators use these basic techniques in their paradigms, and adopt common exposure conditions and test systems, it will be difficult to pinpoint where in the circadian timing system electromagnetic field effects originate.

With regard to the significance of field effects, the 1977 report of the National Academy of Sciences indicated that because individuals who are and would be exposed to electromagnetic fields live in natural conditions, subtle effects on circadian rhythms would be overridden by the much more powerful action of natural zeitgebers such as light, temperature, social interactions, feeding cycles, etc. While this is probably true for the majority of humans, there are individuals who have difficulty with circadian synchronization, and their problems could be exacerbated if electromagnetic fields actually do alter circadian rhythms. For example, shift workers (more than 20% of the work force) face temporal environments with conflicting requirements (night workers' family schedules vs job schedules). Another group of individuals who might be adversely affected are those with entrainment disorders. These individuals, both blind and sighted, have difficulty maintaining a 24-h schedule and exhibit what appears to be free-running rhythms. For some reason, the normal temporal cues in the environment are not sufficient to synchronize the circadian timing system of these individuals. A third group of people who could be influenced by altered environmental time cues are those with seasonal mood disorders. If electromagnetic fields do affect the circadian timing system, it could be that individuals who potentially would have problems in these three areas might develop real rhythm disorders in high field environments.

In summary, the current body of research on effects of electromagnetic fields on circadian rhythms indicates:

(1) A variety of circadian systems have been shown to be altered by exposure to electromagnetic fields.

(2) There has been a disturbing lack of uniformity of exposure conditions.

(3) More research should be conducted on rhythm effects so that their significance can be evaluated.

of electromagnetic fields should be examined in a primate model.

CONCLUSIONS

It is difficult to draw general conclusions from the body of published work on electromagnetic field effects on circadian rhythms. The most dramatic results are those of Wever. Unfortunately, no other investigators have used the same field exposure conditions in published studies. There have been only a few studies published in refereed scientific journals, and there has been a marked lack of uniformity on exposure conditions. In toto, it appears that electromagnetic fields may alter the circadian timing system of free-running mammals, but much work remains to be done before these effects are firmly established and their significance evaluated.

It is interesting to speculate on how the circadian timing system could be affected by electromagnetic fields. On the cellular level, it has been proposed that the molecular mechanism for biological clocks involves membrane proteins which--depending on their state of aggregation--alter the ionic environment of the cell (Njus, Sulzman, and Hastings 1974). If this model is correct, then induced currents could charge the feedback between ion gradients and membrane states, thereby directly altering the basic timekeeping system.

On the organismic level, there are several ways that rhythmicity could be influenced by electromagnetic fields. As noted in the Introduction, the mammalian circadian timing system comprises several logically distinct elements. Although any of the elements could be susceptible to electromagnetic fields, the overall importance of these effects would depend on which class of elements is involved. (1) If electromagnetic fields directly affect central neural circadian pacemakers (as Ehret's data suggest) then potentially every rhythmic process in the body could be altered. This could have profound consequences. (2) If mediators or secondary oscillators are affected (as may be suggested by Wever's data) those processes which are downstream in the flow of temporal information would be altered, but these effects would probably be limited to specific physiological system. (3) If merely the expression of a rhythm is affected by electromagnetic fields then the effects on the timekeeping mechanism would be minimal.

Over the years, techniques have been developed with which these various levels of rhythm alteration can be evaluated. These techniques involve testing organisms in the absence of photic zeitgebers and monitoring multiple

CONCLUSIONS AND SUMMARY

The neuroendocrine system regulates most functions of the body and is primarily responsible for the adaptation of living organisms to their environment. As such, it would represent logically a key system in which to detect effects of ELF fields and to study their impact on homeostasis and survival. Notwithstanding its importance, it has received little attention so far, except for independent studies of neurophysiologic responses and hormonal parameters, without any attempt to integrate neuroendocrine signals and to relate these signals to the ability for adaptation to the environment.

The neurophysiologic data reveal a number of effects of ELF fields and suggest some common mechanism of action involving the membrane but fail to correlate these cellular and molecular changes to specific functional consequences (except in the case of phosphenes and retinal stimulation). The endocrinologic data are limited primarily to measurements of circulating levels of hormones for which little valid information can be obtained on the function of the respective endocrine organs. Despite the importance of the cellular mechanisms (possibly) affected by the ELF fields, the suggestions (unsubstantiated) that these fields may act as stressor or (perhaps) may desynchronize some biologic rhythms, with overall consequences on the health and survival of the individuals exposed and their progeny seem, in the light of the available evidence, negligible. However, with the increase in natural and manmade challenges, surveillance of the environment must continue vigorously. In this respect, the study of ELF fields, although revealing no major unfavorable effects so far, should be pursued. Indeed, ELF fields have demonstrated some useful effects (e.g., wound and bone healing), and, if their use is to increase because of military deterrence or technologic advances, it is imperative that their actions be better understood. Hence, the present report has been written (and should be read) as a mild criticism of the (unavoidable due to time and technologic deficiencies) insufficiency of current knowledge; it should be taken as a plea to seek more substantial information by expanding research of the biomedical effects of ELF fields to cover important but still neglected areas of cell communication, neuroendocrine regulations, and developmental and aging processes.

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IMMUNOLOGICAL EFFECTS OF EXTREMELY LOW FREQUENCY ELECTROMAGNETIC FIELDS

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BACKGROUND

In the past decade, both the scientific and public sectors of our society have become concerned with the potential hazards of extremely low frequency (ELF) electromagnetic fields to the environment. The conception of Project Seafarer by the U.S. Navy with its potential for large scale environmental exposure to ELF fields and extensive reports in the Soviet literature concerning the bioeffects of ELF fields have helped manifest this concern and generate a genuine scientific interest in ELF waves. Perhaps the single most important factor in transforming real or imagined ELF fields bioeffects from a societal curiosity to a subject of legitimate scientific concern was the technological revolution which saturated the environment with ELF fields. The steady growth of sources of electromagnetic radiation ranging from large electric generating and transmission plants to the variety of simple household electric appliances has served to significantly alter the electromagnetic background in which we live. The expansion of ELF radiation based technology and our increasing dependency upon this technology has demanded the serious attention of various sectors of society, particularly the scientific community.

A survey of the literature readily displays the wealth of information generated in response to this concern. Documented studies have linked ELF fields to changes in behavioral, neurological, and physiological parameters, as well as to indications of biochemical alterations at the subcellular level (Sheppard and Eisenbud 1977).

Only recently have scientists turned their serious attention to the examination of potential effects of ELF fields on the structure and function of the immune system. Although much data can be found in the literature on the

effects of microwave (MW) intensity and radio frequency radiation on the immune and other physiological systems (Cleary 1977; Dickson and Shah 1983; Glaser 1972), little is available pertaining to ELF field effects on physiology of the immune system. Published research demonstrates a variety of results, much of which has lead to the use of the term "Cheshire Cat Phenomenon" in describing the irreproducibility of some observations (Graves, Long, and Poznaniak 1979). Early immune studies using low frequency fields focused mainly on changes in cell numbers observed following various regimens of whole-body exposure. Only recently have studies addressed the question of ELF field effects on immunological functions. This apparent disinterest in the immune system is somewhat surprising, since there are several reasons to indicate that this system would be a sensitive, measurable target of physiological perturbation by ELF fields.

The immune system is comprised of a complex interacting network of lymphocytic and monocytic cells whose differentiation and functions are exquisitely regulated by cell surface receptor-binding lymphokines and monokines (Jerne 1974). Immunological function is expressed by secretion of molecules such as antibodies or interferon in some cases and by cellular effector mechanisms such as cytotoxic T-cells and NK cells in other cases. While the mammalian host has evolved a diverse set of immunological defenses to deal with the various insults from foreign agents, it is now clear that these diverse systems are intricately interrelated and perturbation of one component or system frequently has significant effects on others. For instance, the thymus-dependent T-cell system regulates the antibody response by B cells through T-suppressor and T-helper functions (Singer and Hodes 1983) and any alterations of T-cell populations will have a major effect on the antibody arm of immunity.

In addition to being internally regulated, the immune system is responsive to other physiological systems of the host. The endocrine system has a major influence on the distribution and function of immune cells and may play a significant role in generating an ordered response to foreign agents. A number of studies have shown that changes in core-body temperature and/or circulating glucocorticosteroid levels, due to various types of stress, cause major shifts in distribution of different cell populations of the immune system as well as changes in function (Riley 1981; Yang et al. 1983). Similarly, it is now apparent that the nervous system imposes some control over

the immune system. Exposure of animals to stress, such as intermittent foot shock, causes the release of opioid peptides from central and peripheral sites (Shavit et al. 1984). These peptides have been shown to alter the distribution and function of several immune cells including T cells, NK cells, and granulocytes (Gilman et al. 1982; Mathews et al. 1983; Wybran et al. 1979). Thus, any consideration of the immunological bioeffects of ELF fields must deal with potential indirect effects as well as direct effects on components of the immune system itself.

In the following discussion, we will examine the literature pertaining to immunological responses to ELF field-exposure, first with regard to cell number and distribution and then within the context of immune function. Our discussion focuses on electric, magnetic, or electromagnetic ELF fields ranging in fundamental frequency from 1 to 200 Hz. Indeed, to the best of our knowledge there are no published studies of immunological effects of ELF range fields above 200 Hz. Electric and magnetic field studies will be categorized where appropriate, as will acute and chronic exposure systems. Further, this review will address the effects of ELF fields on the basis of a) influence on immune cell populations and distribution, and b) influence on immunological function.

ELF AND IMMUNE CELL POPULATIONS

Many early reports in the literature focused on cellular elements of the humoral and cell-mediated immune system with particular emphasis on the overall numbers and distribution of these components in the peripheral blood. Several studies suggest that whole-body exposure to extremely low frequency electric or magnetic fields influence the balance of cell populations of the immune system (Barnothy 1964; Blanchi et al. 1973; Cerretelli et al. 1979). Until recently, little attention was paid to the underlying causes or potential functional changes associated with this phenomenon. It is important to emphasize these latter aspects of the immune system, since, as pointed out earlier, the immune network consists of a delicately balanced multicomponent system in which no one component functions mutually exclusive of the others. Thus, in addition to examining the literature pertaining to cellular population changes in response to ELF field-exposure, we will discuss observed or predicted alterations in other physiological systems which may impact on the regulation and expression of immune functions. Since the variety of exposure

conditions make direct comparisons difficult, we may be able to develop an overall pattern of responses to ELF fields by considering the diverse observations within the context of perturbation of immune regulation.

As referenced above, a number of early studies reported alterations in circulating leukocyte numbers including lymphopenia and neutrophilia in response to ELF field-exposure. Although not the first to report such findings, the study by Blanchi et al. (1973) is most frequently cited in the literature. The authors report that both mice and rats exposed to an electric field of 100 kV/m, 50 Hz demonstrated a significant alteration in circulating white blood cell (WBC) populations. Mice exposed to a chronic 9 h "on" 3 h "off" cycle for a total of 55 days (1,000 h) showed a 98.5% increase in neutrophils, a 44.0% increase in eosinophils, and a concurrent 17% decrease in lymphocytes, as compared to control animals. Rats exposed to the same field for a single 6-h period demonstrated a similar leukocytosis and lymphopenia, with neutrophils and eosinophils increasing to 133.3% and 187.5%, respectively, over control values. Concomitantly, lymphocyte levels decreased 25%. It was also noted that in the rats, these levels returned to normal 9-days post-exposure. While the authors were careful to design their exposure system to reduce corona effects and ozone formation, they make no mention of control for noise or vibration which, as nonspecific stressors, could influence immunological parameters.

The authors offered no conclusions as to the mechanisms of acute or chronic ELF field-induced alterations in numbers of circulating WBC and measured no other parameters such as temperature or serum glucocorticosteroid levels, which will influence the ratio and number of circulating WBC (Yang et al. 1983). Nevertheless, this work served to stimulate a quick succession of studies on this topic, in part because of the limited scope of the results presented, and partly as an attempt to establish this phenomenon as a tangible effect of ELF electromagnetic fields.

Cerretelli et al. (1979), in a more thorough study, was able to duplicate Blanchi's results in rats (1973). Rats were chronically exposed to an identical 100-kV/m, 50-Hz electric field for periods ranging from 30 min to 8 h/day for up to a total of 2 to 8 weeks. A significant increase in circulating neutrophils and decrease in lymphocytes was noted under all exposure conditions. They also indicated that this condition persisted for up to 7-weeks postexposure. In contrast, exposing dogs to a 10- or 25-kV/m, 50-Hz

electric field 8 h/day for a period of 2 to 7 weeks did not alter the levels of circulating neutrophils or lymphocytes. However, other changes in blood parameters, such as reticulocytosis and increased serum proteins were evident in 25-kV/m treated dogs.

Since different species respond differently to stress, care must be taken in interpreting such results. Secondary changes due to stress-related phenomena, such as simple handling, has been shown to alter hematologic and immune characteristics (Riley 1981). A case in point is the observation of Yang et al. (1983) that moving hamsters from one room to another was sufficient to cause an increase in rectal temperature by approximately 1.5°C. Similarly, Hackman and Graves (1981) reported that changes in the environment of mice, such as movement, socially mixing, and exposure to high level noise, caused a 2 to 3 fold increase in circulating glucocorticosteroids over controls.

In the case of the results of Cerretelli et al. (1979), the differences in hematological responses of rats and dogs to ELF field exposure may be in part due to characteristic species responses to handling or changes in environment. Dogs are conditioned to handling and would be less responsive to this type of stress. Alternatively, since these were chronic exposure studies, it is possible that dogs had adapted to the electric field by the time they were tested. Despite the fact that the exposure systems in Blanchi et al. (1973) and Cerretelli et al. (1979) studies may have generated a stress related response, it is doubtful that this could account for the observed changes in leukocyte populations. Stress related steroid changes and subsequent alterations in leukocyte distribution are generally short-lived (i.e., a matter of hours) after exposure to the stressor (Liburdy 1979; Yang et al. 1983). In contrast, the altered leukocyte distribution in response to ELF fields persisted for 9-days and 7-weeks postexposure in the studies cited above (Blanchi 1973 and Cerretelli et al. 1983 respectively).

Ragan et al. (1979) reported a much different result than Blanchi et al. (1973) and Cerretelli et al. (1979). These authors evaluated a large number of hematologic and serum chemistry parameters in both rats and mice. Mice were exposed to an unperturbed 100-kV/m electric field for 21 h a day for as long as 120 days. Following a 60-day exposure, mice showed a significant decrease in circulating neutrophil and lymphocyte levels. However, a replicate experiment demonstrated an opposite effect, with these cell levels being higher than controls. Upon combining the replicate data, no significant

differences as compared to controls could be shown. Similarly, rats chronically exposed for 15 days had a reduction in leukocyte levels; but the replicate demonstrated no statistically significant differences. These authors concluded that no unequivocal evidence exists that electric fields of this intensity can predictably alter blood components. Although neither predictable nor reproducible, significant changes in leukocyte profiles were observed by these investigators. The apparent alteration in results from one experiment to the other might be related to subtle differences in animal physiology, electric field dosimetry, or exposure conditions. The need for standardized verifiable animal population and exposure systems is evident from these experiments.

While there is no evidence that the above described varied responses to ELF field exposure could be attributable to different stress loads or different responses to stress, it is a subject that must be considered in examining ELF bioeffects. It has long been recognized that stress can alter peripheral blood leukocyte profiles in a variety of species (Schalm, Jain, and Carroll 1975). Stress-related diseases as well as the "flight or fight" response are capable of causing a sudden increase in circulating blood corticosteroid levels. These hormones, in particular adrenocorticotrophic hormone (ACTH), have a profound effect on the blood cell components of the immune system (Liburdy 1979; Yang et al. 1983).

These conclusions have been supported by a number of studies reporting changes in serum glucocorticosteroid levels and circulating leukocyte profiles in response to whole body microwave exposure. Liburdy (1979) showed that mice exposed to a microwave field exhibited a marked neutrophilia and lymphopenia. Concomitant with this change in cellular ratios was an increase in splenic T and B lymphocytes. This effect could be reproduced by injection of glucocorticosteroids. Yang et al. (1983) showed that a transient suppression of hamster splenic natural killer-cell activity coincided with increases in plasma glucocorticosteroid levels and altered circulating leukocytes, beginning one hour posttreatment and returning to normal 8 to 10 h later.

Similarly, Smialowicz et al. (1983) demonstrated suppression of splenic NK cell activity in mice that lasted for 24-h postexposure. Treatment of mice with hydrocortisone mimicked the suppressive effects of microwave exposure supporting the contention of Yang et al. (1983) that the observed suppression

was the result of homeothermic-based physiologic changes in the endocrine system.

Although it is not our intent to imply that surface acting ELF fields and tissue penetrating microwaves are perceived mechanistically the same by an animal, these studies point out the parallels in the underlying responses to these two different types of fields. It is generally agreed that many immunologically related effects of microwaves are of a thermal nature, with most effects being related to the deposited heat load experienced by the animal. Although nonpenetrating and apparently not capable of causing significant increases in body temperature, high intensity electromagnetic fields apparently can be perceived by some mammals resulting in stress type physiological changes (Rosenberg, Duffey, and Sacher 1981).

Hackman and Graves (1981) reported that mice exposed to a 60-Hz electric field up to 50 kV/m for 5 min to 6 weeks showed an acute increase in circulating glucocorticosteroid levels lasting a matter of minutes after the onset of a high electric field. In these studies the authors carefully controlled for noise and social stress. Indeed, the importance of this was demonstrated by their observation that, in contrast to ELF effects, the glucocorticosteroid levels increased markedly in response to stressors such as moving, social mixing, or exposure to high level noise (100 dB). Hackman and Graves (1981) also reported that mice adapted rapidly (15 min) to acute electric field exposure and demonstrated no glucocorticosteroid elevation in response to chronic exposure. In contrast, acute exposure studies showed no adaptation to a stronger stressor such as noise. The authors concluded that electric field exposure represents a low-level stress to which animals are capable of rapidly adapting.

Since external stimuli, such as those described above, can be collectively termed "nonspecific stressors" (i.e., reactions independent of the type of stimulus generating a response), the degree of intensity may be the only distinction that separates clear effects seen with microwave research and the inconsistencies seen with ELF field studies. It can be argued that positive data reported on the alteration of circulating cell populations by ELF fields are indeed real, although as yet unexplained. Even the highest intensity ELF fields may still represent the lower threshold of perceived stress, with experimental and animal variation representing the variable that gives us the occasional positive result. For instance, improper dosimetry or failure to

control for corona effects, ozone formation, noise vibration, or animal social behavior could collectively produce a stress level capable of causing physiological responses which ELF would not cause independently.

ELF FIELDS AND IMMUNE FUNCTION

Published studies have addressed this area of concern and have involved both in vitro and in vivo exposure systems. The former deals most often with lymphocyte blastogenesis, a standard measure of cell responsiveness to plant lectins, which serves to mimic normal in vivo reaction to a foreign antigen. These studies attempt to measure a direct effect of ELF fields on lymphocyte membrane interaction with both antigen and soluble mediators as well as the cells' ability to synthesize and replicate DNA.

The latter category focuses more on an animal's ability to respond to in vivo administered antigens or to recover from an antigenic challenge while being subjected to whole-body exposure. Typical of such experiments is the injection of a pathogen followed by a comparison of LD_{50} values (i.e., dose lethal to 50% of the experimental animals) for exposed and sham-exposed groups. More current protocols have employed measures of individual responses of immune system components, allowing for a more indepth analysis of specific areas of ELF field interaction.

The following section will examine the current literature available on ELF fields on immune functions.

In Vitro Studies: A number of results have been reported in the literature that suggests an effect, either stimulatory or inhibitory, on in vitro cultured cells exposed to various levels of ELF fields (Frazier, Andrews, and Thompson 1976; Tenforde 1979). Included in this type of work are studies of peripheral blood cells and their reaction to a stimulus while under the influence of an electric and magnetic field. The ability of lymphocytes to mitogenically respond to plant lectins have made them a natural model to study what effects ELF fields may have on cellular control and function.

Conti et al. (1983) explored this question in detail. Human peripheral blood lymphocytes were isolated and prepared for an experiment involving a combination of mitogens and ELF field levels. The three mitogens used were concanavalin A (Con A) and phytohemagglutinin (PHA) (both T-cell mitogens), and pokeweed mitogen (PWM) which stimulates B-cells as well as certain subsets of T-cells (Hood, Weissman, and Wood 1978). Employing electromagnetic fields

th frequencies from 1 to 200 Hz and a variety of exposure times, Conti et . (1983) demonstrated an inhibitory effect on the blastogenic response of mphocytes to all mitogens. Furthermore, they reported that while PHA stimu-tion was inhibited at all frequencies tested, the Con A- and PWM-induced astogenesis was suppressed only at the lower frequencies. They attributed is difference to the possibility that the various mitogens were stimulating fferent subsets of lymphocytes with different sensitivities to graded fre-encies of ELF fields. While this could explain the different responses to IA and PWM, there is little information on the possibility that PHA and Con A imulates separate T-cell subsets. With the current knowledge of T-subset ecific cell surface markers and the availability of antibodies to deplete lected subsets, it should be possible to determine if there are T- or B-cell bset differences in sensitivity to ELF field exposure. This could be of jor significance if one considers the important role of T-suppressor and helper cells in regulating the immune response (Singer and Hodes 1983).

Conti et al. (1983) suggested that ELF field effects on the inhibition of mphocyte responsiveness to mitogens was the result of an electrochemical chanism, altering Ca^{2+} flux across the plasma membrane. This is a plaus-le explanation, since it is well established that Ca^{2+} is an essential ssenger in triggering many cellular responses, including that of lymphocytes eltzin et al. 1983). In support of this, Bawin and Adey (1975) demonstrated at at 6 and 16 Hz, a 10- and 56-V/m field frequency caused decreased efflux Ca^{2+} from a number of cell types, possibly by blocking the Ca^{2+} annels. This is consistent with the observed suppression of lymphocytes to togen-induced blastogenesis, since increased cytosolic Ca^{2+} is required r the mitogenic response (Maino, Green, and Crumpton 1974).

There are alternative explanations for the results of Conti et al. (1983), st notably the possibility that exposure of lymphocytes to ELF fields alters e number or expression of mitogen receptors on the cell surface. In this gard, Smith, Knowlton, and Agarwal (1978) reported that exposure of lympho-tes to MW frequency fields reduced the number of surface receptors for Con and Sultan, Cain and Tompkins (1983) reported that MW exposure suppressed e ability of B-cell surface immunoglobulin (Ig) to be redistributed by ti-Ig. In the latter case the effect was attributed to thermal effects of , which would not appear to be a significant component of the ELF field posure system. Although Conti et al. (1983) monitored pH in their exposure

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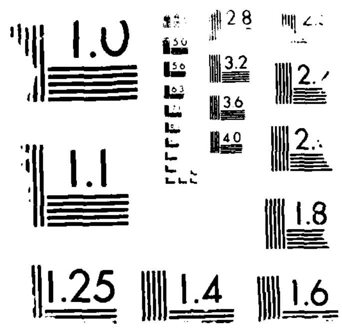
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system, they made no mention of temperature measurements. While these are attractive hypotheses, additional well-defined studies are required to provide an explanation for the observations of Conti et al. (1983).

In Vivo Studies: Some of the simplest in vivo studies involving wholebody exposure and immunity consisted mainly of measuring an animal's ability to recover from an infection. These experiments evolved as the apparent next step, following reports by various investigators concerning a postexposure decrease in circulating lymphocytes (Barnothy 1964; Blanchi et al. 1973) as well as altered serum chemistry (Marino et al. 1976), as discussed in the previous sections.

As early as 1965, Odinstov reported on the immune functions of mice infected with the bacterium Listeria monocytogenes, following both acute and chronic exposure to ELF fields. Animals were exposed to a 200 oersted magnetic field at a frequency of 50 Hz for 6.5 h (acute) or 6.5 h daily for 15 days (chronic) and then injected intraperitoneally with varying concentrations of the bacterium. Resistance was based on four criteria including LD_{50} values, microbe distribution in organs, phagocytic activity of leukocytes, and the overall leukocyte number. The results for the acute exposure indicated no significant difference in any of the parameters measured from that of controls. However, chronic exposure caused a significant negative result in all areas measured. Leukocyte phagocytic function decreased by approximately 40%, organ bacterial counts were higher, and LD_{50} values for exposed groups were 20% lower than controls. The authors concluded that the animal's resistance was impaired following chronic ELF field exposure and that this impairment could be attributed to a decreased antibacterial activity of leukocytes.

The results of Lantsman (1965) would appear to support the contention that ELF field exposure suppresses cellular phagocytic function. Mice were exposed 8 h daily for 4 days to a 200-C, 50-Hz magnetic field. While details are lacking, the author reported a significant inhibition of phagocytic function of the reticuloendothelial system in several organs. Whether or not this observation was from in vivo blood clearance studies was not stated.

In contrast to the above studies, Cerretelli et al. (1979) reported no significant change in the resistance of albino mice to Staphylococcus pyogenes, following chronic ELF field exposure. The animals were exposed 8 h/day at 25 kV/m over a period of 42 days. The mice were then injected

intraperitoneally with the bacteria and the number of deaths recorded up to 72 h, the time at which the LD_{50} was expressed. The dose of bacteria found to be lethal to 50% of the exposed animals was equal to that of the nonexposed controls, indicating no effects produced by these exposure conditions.

In a similar study, Krueger and Reed (1975) examined the effect of a 21-day exposure at 100 V/m, 75-Hz electromagnetic field on the resistance of mice to influenza virus. Animals were challenged intranasally with the PR8 strain of influenza virus following exposure, and the resulting LD_{50} values recorded. As was the case with the results of Cerretelli et al. (1979), no observable change in resistance was noted in the exposed animals.

Failure to employ standard challenge systems makes it difficult to compare the results of the above cited studies. For instance, L. monocytogenes is an intracellular replicating pathogen, whereas S. pyrogenes is not, and usually different components of the cell-mediated immune and phagocytic systems are responsible for the their clearance. The polymorphonuclear leukocyte may provide the primary control mechanism for S. pyrogenes, whereas, the activated macrophage is more important for L. monocytogenes clearance. Similarly, influenza virus is handled by the immune system in a completely different manner. Effective control will depend to a large extent on the alveolar or inflammatory macrophage or stimulations of the specific cell-mediated or humoral immune system. Thus, Krueger and Reed (1975) may have induced a suppression of leukocyte phagocytosis as reported by Odinstov (1965) and Lantsman (1965) but would not have registered such a change by challenge with influenza. Comparisons of these challenge systems are further complicated by the evidence suggesting that fatalities to influenza virus administered intranasally is due to acute inflammatory responses in the lung rather than tissue damage by the virus per se.

The above studies failed to consider any of these distinguishing characteristics of the immune response to various pathogens and as a result, although they have merit by themselves, do not contribute to the overall understanding of putative ELF field effects on the immune system.

Morris and Ragan (1979), using a whole-body exposure system, went further than previous investigators in an attempt to measure more direct immune components of mouse peripheral blood. Aside from observing alterations in the levels of humoral and cell-mediated components, specific immune functions were studied. Animals were exposed to a 100-kV/m, 60-Hz electric field for

21 h/per day for either 30 or 60 days. Following this treatment, serum immunoglobulins, complement activity, T and B cell distribution, and leukocyte levels were measured. To measure serum antibody responses, animals were challenged intraperitoneally with 5 mg of keyhole limpet hemocyanin (KLH) immediately after an exposure period, and then returned to the field for 14 days prior to measuring antibody levels with an immunoprecipitation technique. Being a T-dependent antigen, KLH can effectively demonstrate competent T- and B-cell cooperation, a necessary prerequisite to the maturation of proper antibody production and affinity.

To study complement activity, serum from exposed animals was collected and mixed with sheep red blood cells coated with rabbit anti-sheep antibody. Compared to a guinea pig complement standard, the degree of hemolysis measured activity. Enumeration of T- and B-cell levels in peripheral blood was measured by using fluorescent antibody labeling of B cells, and a spontaneous rosette assay with sheep red blood cells was used to measure T cells. Blood smears were stained with Wright-Geimsa for leukocyte differential counts.

Given the variety of assays performed following these exposure conditions, only one statistically significant result was observed. In the 60-day exposed group, both leukocyte and lymphocyte concentrations were lower as compared to the sham-exposed group. However, the authors report that in a replicate experiment, leukocyte and lymphocyte levels were actually higher than the sham-exposed group. Assay results from the functional studies (i.e., antibody production, complement activity) showed no apparent change in immunocompetence.

Using the same exposure levels with slight changes in exposure times, Morris and Phillips (1982) studied the effects of ELF fields on spleen lymphocyte blastogenesis. Unlike the work of Conti et al. (1983), who investigated in vitro effects of ELF fields on human peripheral blood lymphocytes, these authors examined the influence of whole-body exposure on mouse spleen lymphocyte stimulation. Animals were exposed to a 100-kV/m, 60-Hz electric field for 20 h/day for 90 or 150 days with the assay being run immediately afterward. With Con A, PWM, or LPS (lipopolysaccharide, a B-cell mitogen) as the mitogen, the stimulation indices for 90- and 150-day exposed mice did not statistically differ from that of sham-exposed animals. By using the blastogenesis assay as a measure of cellular interaction and immunocompetence, these results indicate no harmful effects produced by these exposure conditions on either T or B lymphocyte numbers or function.

Thus, a summary of the last two studies cited, which appear to be the most comprehensive studies of immunological functions following whole-body exposure to ELF fields, suggests that long-term exposure of ELF fields is not measurably detrimental to any immune system tested including: production of normal serum proteins such as complement and Ig; antibody response to T-dependent antigens; T-cell regulatory function of the antibody response; leukocyte distribution; and T- and B-cell numbers and their response to mitogens. While the conclusions from these experiments appear self evident, they should be tempered by the observation that the data is derived from only a few experiments, employing a limited number of ELF field-doses, exposure times, assay times, and perhaps not always the most sensitive assays of immune function.

SUMMARY

This review has attempted to evaluate the available literature evaluating the effects of ELF fields on immune cell populations and functions. Most early research focused primarily on alterations in cell populations with little emphasis on function. A number of studies demonstrated ELF field-induced neutrophilia and lymphopenia under both acute and chronic exposure conditions. While the underlying causes of these leukocyte changes have not been investigated, they may be attributable to changes in the physiological systems regulating immune cell populations.

Changes in the hormonal balance of the mammal have powerful consequences on the immune system. Prolonged stress-related increases in glucocorticosteroid levels cause a variety of immunological alterations, including neutrophilia and lymphopenia as well as changes in immune function.

While the observed changes in leukocyte distribution reported in response to ELF field exposure could be due to changes in such systems as circulating glucocorticosteroids, existing data indicate that this is not the direct result of the ELF field. For instance, ELF fields neither causes dramatic temperature changes nor marked alterations in steroid levels. Second, steroid responses to ELF waves have been reported to be mild and transient, whereas the leukocyte effects have been prolonged after exposure. A more likely explanation for the observed positive effects of ELF fields on leukocyte population is a cumulative nonspecific stressor phenomenon due to inadequacies of the exposure system. Inadequate care for ELF field dosimetry and side effects such as ozone formation and corona effects and animal handling may

generate stressor responses unrelated to the ELF field itself.

Immune function studies, like that of the cell population studies, demonstrated no definitive effects produced by ELF fields. The in vitro studies measuring blastogenesis of human lymphocytes under an electric field produced some inhibitory results, depending on the mitogen and frequency used. An electrochemical mechanism leading to perturbation of the plasma membrane and affecting calcium efflux was postulated as the cause of this inhibition. These results may have been a peculiarity of the in vitro exposure system, since they were not reproduced when lymphocytes were tested from animals exposed to ELF fields.

In vivo studies involving mice experimentally challenged with various pathogens produced mixed results, with differences in LD_{50} values between treatment and controls being the standard measurement of resistance. The differences cited could possibly be attributed to the difference in exposure conditions and/or pathogens used.

Finally, studies have been done that more directly addresses immuncompetence and ELF fields. This work examined the functional capability of the mouse immune system following chronic long-term exposure to electromagnetic fields. No reproducible results involving changes in serum immunoglobulins, complement activity, or T- and B-cell levels were reported. A lymphocyte blastogenesis assay, used to measure a cell-mediated immune response, did not reveal any effects produced by ELF fields.

The work analyzed in this paper by no means represents a final unequivocal answer to the question of ELF field perturbation of immune systems. On the contrary, it should serve to point out the deficiencies inherent in a research area of such diversity. First, like that of microwave research, it is hoped that some standard exposure conditions and immunological challenge systems can be set that will allow for better and easier comparison of results. Second, it is important that care be taken to assess potential alterations in other physiological systems that may impact on the immune system.

In conclusion, the data reviewed in this paper suggest that exposure to ELF fields can cause alterations in the immune system, although generally transient and mild in nature. We interpret this to indicate that ELF field exposures represent a near threshold "nonspecific stressor" phenomenon to which the response is, by definition, unpredictable and subject to individual, as well as, species variation. Future studies employing highly controlled

exposure systems and more sensitive and sophisticated measures of immunological functions may provide more predictable indicators of potential ELF field bioeffects.

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NEURAL EFFECTS OF EXTREMELY LOW FREQUENCY FIELDS AS A FUNCTION OF INDUCED TISSUE CURRENT DENSITY

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INTRODUCTION

Communication in the nervous system takes place largely in the form of electrical signals whose bandwidth falls between 0 and 10,000 Hz. This includes the Extremely Low Frequency (ELF) range of interest in the American Institute of Biological Sciences (AIBS) study. ELF electric currents can therefore be expected to have an influence on neural function if they are sufficiently intense. There exists, however, considerable controversy as to what constitutes a sufficiently intense current (i.e., electromagnetic field strength).

It has long been known that 60-Hz tissue current densities of the order of 10^{-3} A/cm^2 (i.e., mA/cm^2 range) or more can have immediate and profound effects on electrically excitable tissue (e.g., electric shock sensation, involuntary muscle contraction, and cardiac fibrillation leading to electrocution). The basis for this can readily be seen using either in vivo or in vitro preparations in which intracellular recording is achieved. The intracellular recording technique has also proved valuable recently in showing that somewhat weaker currents (from 10^{-3} down to 10^{-6} A/cm^2) can also have a direct, immediate effect on neural firing patterns. Such effects can be reconciled with the electrophysiological properties of autorhythmic (i.e., pacemaker) neurons. On the other hand, reported effects of ELF electric currents that are extremely weak (10^{-6} down to 10^{-9} A/cm^2) take on a different nature (such as changes in calcium efflux) and are harder to associate with neuroelectric signaling processes. Also, it is fair to say, there is much less agreement in the literature as to the occurrence of these effects and their significance than there is at the higher current density levels (above 1 μA/cm^2).

In this report I will present an overview of the evidence for neural effects at these three levels of tissue current density (i.e., the milliamp,

icroamp, and nanoamp levels) and also attempt to show where similarities or isparities of underlying actions may exist. Also, in keeping with the rimary purpose of the AIBS study, I will try to relate these purported ffects (mostly in vitro situations) to the possible impact they might have on uman ELF field exposure situations.

. WHY USE TISSUE CURRENT DENSITY (A/cm^2) AS THE PRIME INDEX OF ELF EXPOSURE?

This is a good question--especially from the standpoint of the reader who s concerned with external field strengths such as those found near power ransmission lines or ELF antenna arrays. The answer is both simple and omplex. The simple version is that it is easier to control and measure urrent density than other electromagnetic field parameters. For example, the xternal electric field strength needed to induce (by capacitative coupling) a iven current density in isolated brain slices will depend on the geometry and lectric properties of the tissue chamber (and perfusion system) used. This xternal field will also differ considerably from the field needed to produce he same current density (and thus, in general, the same effect level) in the orresponding portion of the brain of an intact animal. Likewise, the tissue urrent density (TCD) produced in the brain of intact animals in an ELF field ill vary widely depending on the animal's species, position in the field, osture, etc. Table I shows the approximate brain TCDs that would likely be nduced in a standing human in external (i.e., unperturbed) ELF electric ields of 10^7, 10^4, and 100 V/m. A rough "rule of thumb" for relating xternal field strenghts to neural TCDs in standing humans is that a 10-kV/m ield in air can be expected to lead to about 10^{-6} A/cm^2 TCD in the head

Table I Approximate (to nearest order of 10) TCD produced in head of erect humans in 60-Hz electric fields.

Unperturbed Electric Field Strength (V/m)	Tissue Current Density in Head Region (A/cm^2)
10^7	10^{-3}
10^4	10^{-6}
10^2	10^{-9}

dges and Preach 1982; Deno 1975). However, it must be borne in mind that this rough estimate can change drastically for different animal exposure litions and it does <u>not</u> apply to the in vitro experimental cases.

The more complex reason for referring to TCD as the prime index of ELF metry is that electrophysiological responses at the neuronal level depend on ily localized voltage gradients (such as those across or along the cell orane) which are often hard to measure directly but can be estimated from the ue current density. Furthermore, the extent to which a nerve (or muscle) will respond to an electromagnetic field appears to be a function of the that the field produces immediately around that cell (as opposed to the erall" current density in the brain or other organ of interest). This croscopic aspect" of the neural effects of ELF currents can best be seen by king at "electric shock" levels (TCD above 10^{-3} A/cm^2) and extrapolating nwards.

EFFECTS ON HIGH DENSITY ELF CURRENTS ON EXCITABLE CELL FUNCTION (TCD ABOVE 10^{-3} A/cm^2)

A variety of effects of intense currents are well known both to roscientists and those unfortunate enough to be exposed to electric "shock" uations. Table II, which is taken from the work of Dalziel (1972),

Table II Estimates of 60-Hz tissue current density (TCD) associated with various "electric shock" phenomena.

	(Amps) Total Current	(cm^2) Effective Area	(A/cm^2) Equivalent TCD
Perception in Fingertips	10^{-3}	1	10^{-3}
Cannot-Let-Go	10^{-2}	10	10^{-3}
Cardiac Fibrillation	10^{-1}	100	10^{-3}
Cardiac "Microshock"	10^{-5}	10^{-2}	10^{-3}

Dalziel 1972.

l) to comment on the elusive nature of effects ascribed to very weak ELF lds.

Two questions occur to me when considering the significance of the neural ects associated with very weak ELF fields:

1. Can a neural effect be so ephemeral and still be real?
2. What is the likely impact of this phenomena on brain function (i.e., electrical and chemical signal processing)?

The answer to the first question is probably yes. It is the very nature of brain to respond differently to similar exogenous inputs, depending on its internal state. This principle can be seen to act even in the case of the rementioned _Aplysia_ synchronization phenomena. An _Aplysia_ pacemaker neuron --by slightly shifting its ambient firing rate--become far less sensitive an imposed ELF field and the induced-state of synchrony can disappear like "Cheshire Cat". It stands to reason that the chick brains used in the cium efflux studies have far more complex, seemingly erratic, internal tes than do single _Aplysia_ neurons. The appearance of amplitude, frequency, other "windows", as well as the difficulty of reproducing the same results different laboratories, could be attributed to variability in ambient brain ivity.

The answer to the second question is more elusive--it really depends on re the calcium is coming from and going to with regard to the neuronal ieu. Since the internal concentration of free calcium ions in most nerve ls is maintained at very low levels (about 10^{-7} moles/liter) small ements of calcium into the neuron from extracellular spaces can and do have or effects on neuronal function; such as inducing long-lasting membrane duc- tance increases, releasing of neurotransmitters, and changing ion-potential generation (Kandel 1976). Appreciable effects could also be ected to result from changes in calcium bound to the cell membrane face. On the other hand, if the calcium was moving from one extracellular mpartment" to another then the effect on neuronal function would not be y significant.

CLUSION

In adjudging the impact that ELF fields might have on neural function in a an exposure situation, we must consider the probability of an effect urring in simpler situations.

essentially no effect was seen. This effect is thus clearly dependent on field orientation (Sheppard, Burton, and Adey 1983). A similar effect of sinusoidal currents was also noted wherein the direction of the effect-polarity depended on the phase of the sine wave during which the slice was stimulated.

2. Long term potentiation (LTP) of the evoked response (which would persist for several minutes after the field was turned off) could be produced by ELF fields of 20- to 50-mV/cm intensities. However, in this case, it did not matter what orientation the field was at with respect to neuronal axes (Bawin et al. 1984).

One explanation for these somewhat dichotomous results (with regard to field orientation effects) is that the sites of action for the LTP effect are the presynaptic terminals which have a wide dispersion of anatomical orientations whereas the shorter term (DC field) effect is based on direct excitation influence of the CA1 neurons which are organized in parallel columns.

IV. NEURAL EFFECTS OF VERY WEAK ELF CURRENT (TCD) BELOW 10^{-6} A/cm^2)

In this range it is difficult to argue for direct effects on neuronal firing patterns, especially since the spontaneous fluctuations (i.e., noise) in transmembrane currents are likely to be of a higher density than the ones imposed (Kandel 1976). However, somewhat indirect evidence for neural effect has been put forward by two well-established laboratories (Bawin and Adey 1976; Blackman et al. 1982) in the form of changes in brain calcium efflux. These studies are well known and have been reviewed several times so I will not attempt to rehash their detail. The fascinating thing, and the basis for wide controversy emanating from these reports, is the appearance of "windows" (amplitude, frequency, and time) into which the ELF field parameters must fall in order to elicit an effect. Recently, Blackman et al. (1984) has extended these specialized conditions to include the strength and direction of steady background magnetic fields, i.e., the orientation of the applied ELF field with respect to the earth's magnetic field is reported to be an important factor.

Several investigators have raised questions concerning the methodological approach used in these studies (e.g., Myers and Ross 1981) or have reported no effects in similar experiments (Merritt, Shelton, and Chafnes 1982). In addition, some other scientists have used poetic expressions such as "ephemeral" (Sheppard 1984) or "Cheshire Cat Phenomenon" (Graves per comm.

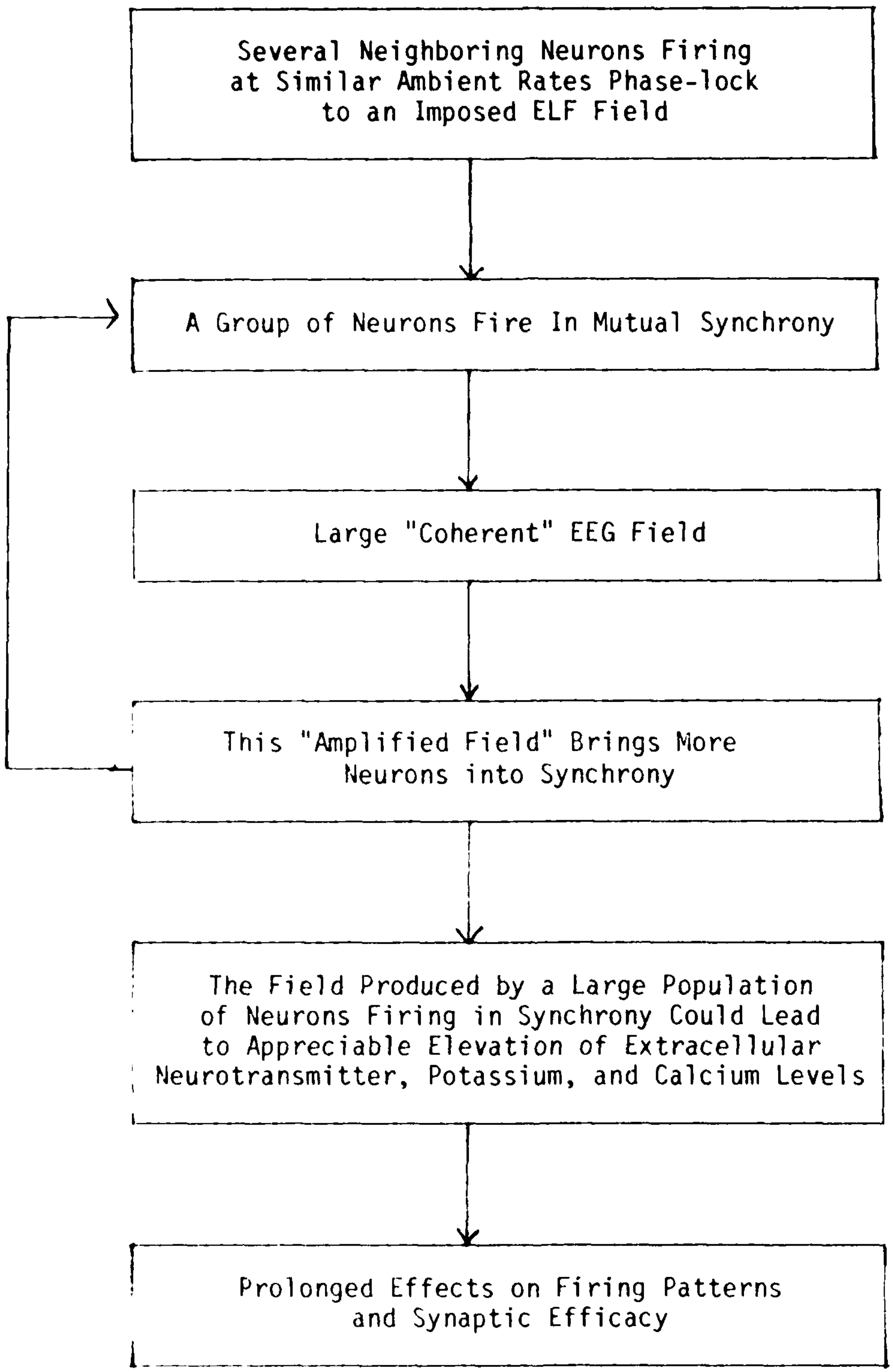

Figure 6. A hypothetical scheme whereby relatively weak ELF fields could cause a "spread of synchrony" over a large population of neurons and possibly lead to long-term changes in neural function.

"intensified field" could then act to bring other nearby neurons into synchrony--even those whose firing rates were initially too far afield to be phased-locked by the exogenous field alone. Thus, these three neurons could act to draw a fourth neuron into synchrony and these four could then pull in a fifth and then a sixth, etc. In this manner the "zone of synchrony" could propagate over large regions of the brain in much the same way as an epileptic focus is thought to spread. Further illustration of this process is shown in Figure 6 in the form of a recurrent sequence of events leading to the spread of synchrony and, possibly, other related consequences.

This hypothetical scheme gains support from some experimental observations of the mammalian brain. First of all, the field gradient for the normal EEG within the brain is on the order of 10 to 100 mV/cm (Adey 1980). This can lead to average current densities of 100 $\mu A/cm^2$ or more. The results of our studies show that this is a sufficient level to produce synchrony among nerve cells. Secondly, a recent study by Taylor and Dudek (1982) has shown that neural afterdischarges in rat hippocampal slices will occur synchronously due to ephaptic (i.e., electric field) coupling. In this study the usual chemical synaptic coupling between cells was blocked (by using a high magnesium, low calcium perfusion solution) and the coupling potentials that lead to synchrony could only be attributed to the summed extracellular field. It is also possible that in this case, as in others, the extracellular potassium concentration around a neuron is raised by the firing activity of nearby neurons and that this contributes to the "nonsynaptic" coupling between neurons. However, this is a relatively slow process and is not thought (by Taylor and Dudek) to be capable of producing the rapid synchronous activity that they observed.

Recent results reported by Bawin et al. (1984) on ELF field induced changes on the evoked responses of rat hippocampal slices may be closely related to the synchrony phenomenon. In these studies electric fields were found to have at least two distinct effects on the evoked response:

1. DC fields 10 to 300 ms in duration and 200 mV/cm in intensity (which produces about 4-mA/cm^2 current density in the brain slice) were found to increase the population spike attributable to the excitation of CA1 pyramidal cells when the field orientation was from the dendrite to the soma. However, when the field was reversed, the population spike decreased. If the field were applied perpendicular to the dendrite-somatic axis

flows into a cell is canceled by the equal amount that flows out through nearby membrane regions. In fact, it is only because a nerve cell is asymmetric with respect to the effect of currents flowing in opposite directions that it can be affected by an extracellular current at all. These two factors (extracellular shunting and cancellation of opposing membrane currents) are likely to be highly dependent on the direction of the current with respect to the neuron's orientation and could explain the directional sensitivity of J_f effects. A field theory analysis of such an orientation effect has also been put forward by Klee and Plonsey (1976).

If one restricts the phenomenon of ELF synchronization of nerve cells so as to involve only a few scattered neurons that happen to be firing at a rate close to the frequency of the imposed field, then the ELF's impact on overall brain function is likely to be trivial. On the other hand, if the phenomenon had some ability to "propagate itself" so that a large number of neurons could be brought into synchrony, the neurological consequence could be substantial. It is conceivable that such a propagation could occur in populations of nerve cells that are weakly coupled to begin with (as is the usual case), but that can be made to act as a "synchronous focus" by an exogenous field of the appropriate frequency and intensity. To illustrate this possibility, consider the three-neuron aggregate shown in Figure 5a. Let us assume that these three neurons are weakly coupled to each other by excitatory synapses and that they fire at ambient rates that are close but not equal to each other (Figure 5b). The extracellular field generated by these three neurons acting collectively can be predicted by summing the excitatory synaptic potential (EPSP) field they produce. This "mini-EEG" will be of relatively low amplitude and quasi-random time course because, in this case, the summation of the PSP fields is incoherent. This sort of field is not likely to induce synchronous behavior in any neighboring neurons.

Now let us assume that an exogenous ELF field is added to this system. If this frequency (or a multiple of it) were close to the average ambient firing rate of the three neurons and its strength was appropriate it could phase-lock all three neurons to itself and thus to each other, as in Figure 5c. The resulting extracellular field (i.e., "mini-EEG") would be characterized by relatively intense summed EPSP fields occurring in synchrony with the applied ELF signal. Such a neurally-generated field could be more intense (i.e., lead to higher current densities) than the exogenous field which caused it. This

current levels to be sufficient and report that levels of about 60 $\mu A/cm^2$ are needed. Whether this discrepancy is based on their improved methodology or on our probing for maximum sensitivity directions remains to be resolved. Both sets of results show, however, that relatively weak intracellular ELF currents (down to 0.1 nA) can produce clear phase-locking effects and that extracellular ELF fields produce similar effects at levels that are well below the 10^{-3} A/cm^2 densities that are usually thought to be needed to markedly influence neural function. Obviously these synchrony phenomena were elicited under specific laboratory conditions using a particular set of isolated pacemaker neurons (from Aplysia). The question thus arises whether these phenomenon are generalizable to the intact mammalian brain and whether they bear any useful relationship to other reported neural effects of relatively weak ELF fields. It is also of interest to inquire as to how likely it is that effects such as these could occur as a result of human exposure to ELF fields.

In principle, the transmembrane current density J_m can easily be determined in terms of current density (A/cm^2) across the membrane. It turns out, however, that the membrane area across which these currents flow is difficult to measure and subject to considerable uncertainty. The membrane area of molluscan neurons, similar to the Aplysia pacemakers used in this study, has been estimated by electrophysiological as well as morphological techniques (Coggeshall 1966; Gorman and Mirolli 1972). For the pacemaker cells used in this study such estimates of membrane area range from 10^{-1} to 10^{-2} cm^2. Applying these figures to the observed minimum injected currents (for the one-for-one synchrony point in Figure 3a) gives a transmembrane current density range from 6 to 60 $\mu A/cm^2$. The geometric mean of these two values (20 $\mu A/CM^2$) is equal to about 1 of the field current density (J_f) needed to produce the same effect (see Figure 2b). This is not surprising when one considers that a great deal of current shunting takes place through the extracellular spaces surrounding the individual neurons.

As mentioned earlier, Schwan (1984) cites a figure of about 1 as the ratio of transmembrane to extracellular shunt current densities, (J_m/J_f), which agrees closely with our original estimate. On the other hand, Sheppard, French, and Adey (1980) compute a lower ratio of (J_m/J_f) for eliciting equivalent effects (about 0.01). Again this discrepancy may be attributable to orientation effects since, to a large extent, the effect of a current that

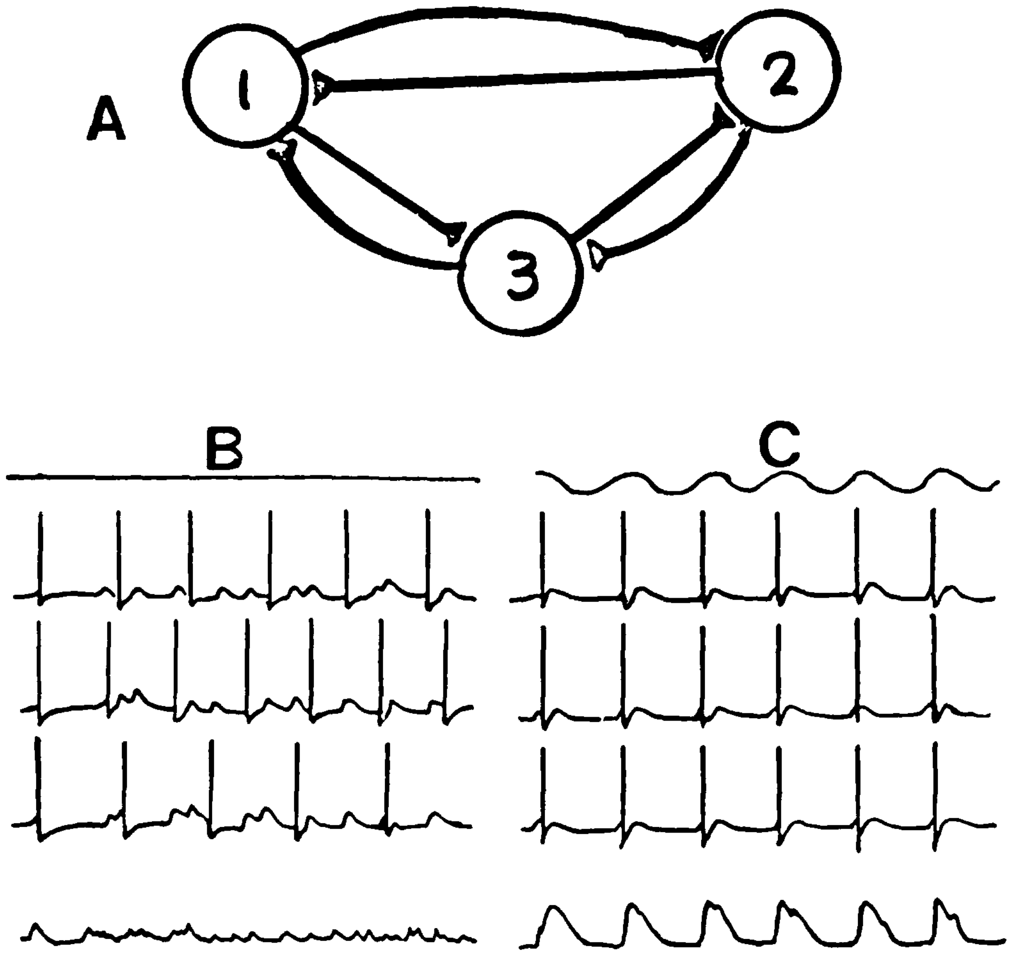

Figure 5. A hypothetical scheme whereby a relatively weak ELF field would synchronize the firing of a group of neurons and thereby produce an intensified extracellular field of the same frequency.

(A) An example of three neurons which are mutually coupled by excitatory synapse.

(B) The firing pattern of the three neurons in the absence of an exogenous ELF field. Ambient firing rates are close to each other but not identical and not phase-locked. The combined extracellular field is therefore "incoherent," of low amplitude, and asynchronous.

(C) The firing patterns of the three neurons after their firing has been captured by an exogenous ELF field. All spikes and EPSPs now occur in synchrony which leads to a surrounding (EEG) field which is "coherent," of large amplitude, and synchronous with all three neurons.

In parts (B) and (C), the first trace is the applied field, the next three traces show the V/m of each neuron, and the bottom trace shows the neurally generated extracellular field.

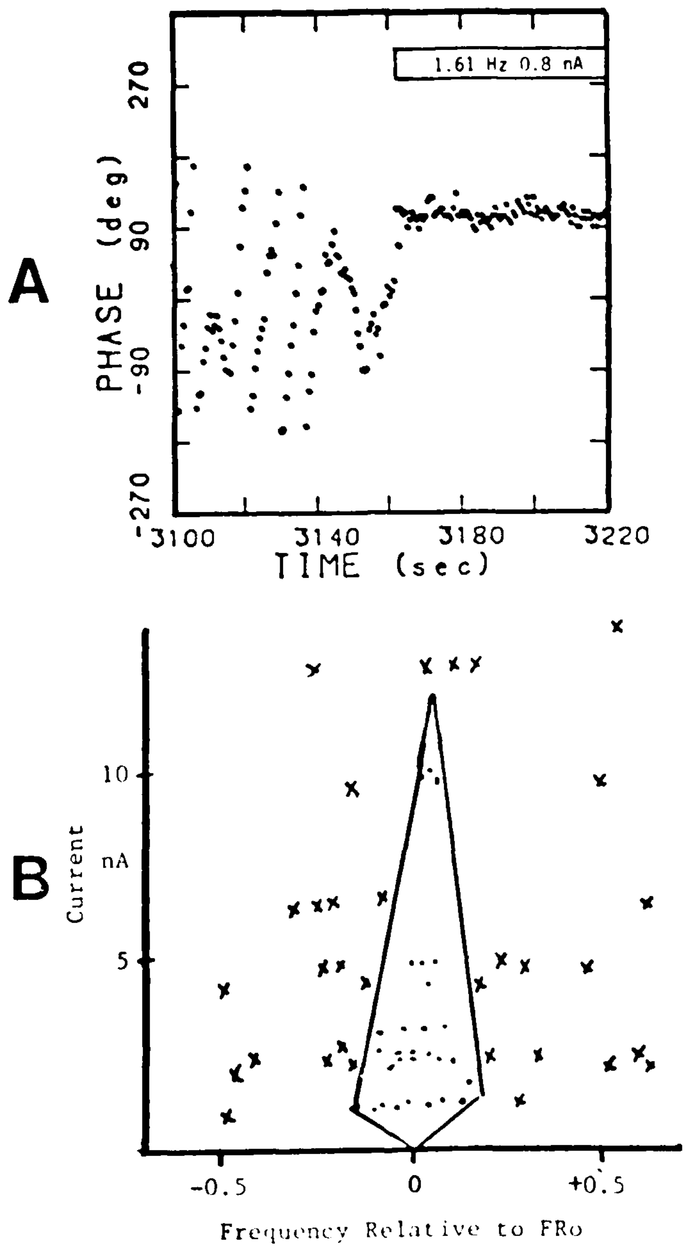

Figure 4. Results of Barnes, Sheppard, and Sagan (1984) studies of neuronal synchronization by ELF intracellular currents. (Reprinted with permission of the authors).

(A) An example of computer-processed neuronal spike phase data showing the onset of one-for-one synchrony in the form of a constant "phase-lock" situation as contrasted with the earlier wandering of the spike phasing.

(B) A distribution of the frequency-intensity combinations (dots) which lead to one-for-one phase-locking of neuronal firing and those which do not (x's). From such data a "diamond shaped" zone into which all one-for-one synchrony producing combinations must fall can be drawn.

multiples or "sub-multiples" of FRo, the threshold currents needed to produce lock-in were substantially higher, as can be seen from the plot shown in Figure 4a. This threshold current rises sharply for ELF frequencies that are several times greater than FRo but then levels out as the synchronization phenomenon is overridden by membrane rectification effects.

In their recent studies Barnes, Sheppard, and Sagan (1984) examine the phenomenon of phase-locking at ELF frequencies close to FRo in substantially more detail. With their more sensitive methods of data analysis, which is illustrated in Figure 5a, they have shown even lower ELF current thresholds than we initially reported. They have also shown, as is illustrated in Figure 4b, that as the ELF frequency is varied from 0.5 x FRo to 1.5 x FRo the thresholds follow a "V-shaped" distribution that can be predicted from a general theory of nonlinear coupled oscillators expounded by Adler (1946). Somewhat more surprising, however, was their finding that synchrony was lost when the ELF current was too strong. This "loss of synchrony" threshold curve forms an "inverted V" distribution around FRo resulting in a "diamond-shaped window" of ELF frequency-intensity combinations near FRo to which the phase-locking phenomenon is restricted. Presumably a similar "window" would exist around higher order modes (i.e., ELF frequencies of 3 FRo, 2 FRo, etc.), but only preliminary evidence for this is available.

In our initial paper (Wachtel 1979), we also reported that the synchronizing effects produced using intracellular ELF current injection could be mimicked with ELF fields applied across the entire chamber and, thus, a corresponding TCD could be determined. In this case, however, it seemed that the direction of the field relative to the axis of the ganglion was an important factor. Rotations of the parallel plate electrodes around the ganglion resulted in sensitivity maximums that were about 10 fold greater than the minimums. Using these maximal sensitivity orientations we generated another curve relating ELF current density threshold to frequency, as is shown in Figure 3b. This curve is quite similar to that in Figure 3a (which was derived from intracellular ELF currents) even though the presence of large field "artifacts" made these data less certain. We reported originally that extracellular current densities (J_f) of as little as 2 $\mu A/cm^2$ were sufficient to produce 1-for-1 synchrony (presumably at maximally-sensitive orientation).

Sheppard, French, and Adey (1980) have not found these extracellular

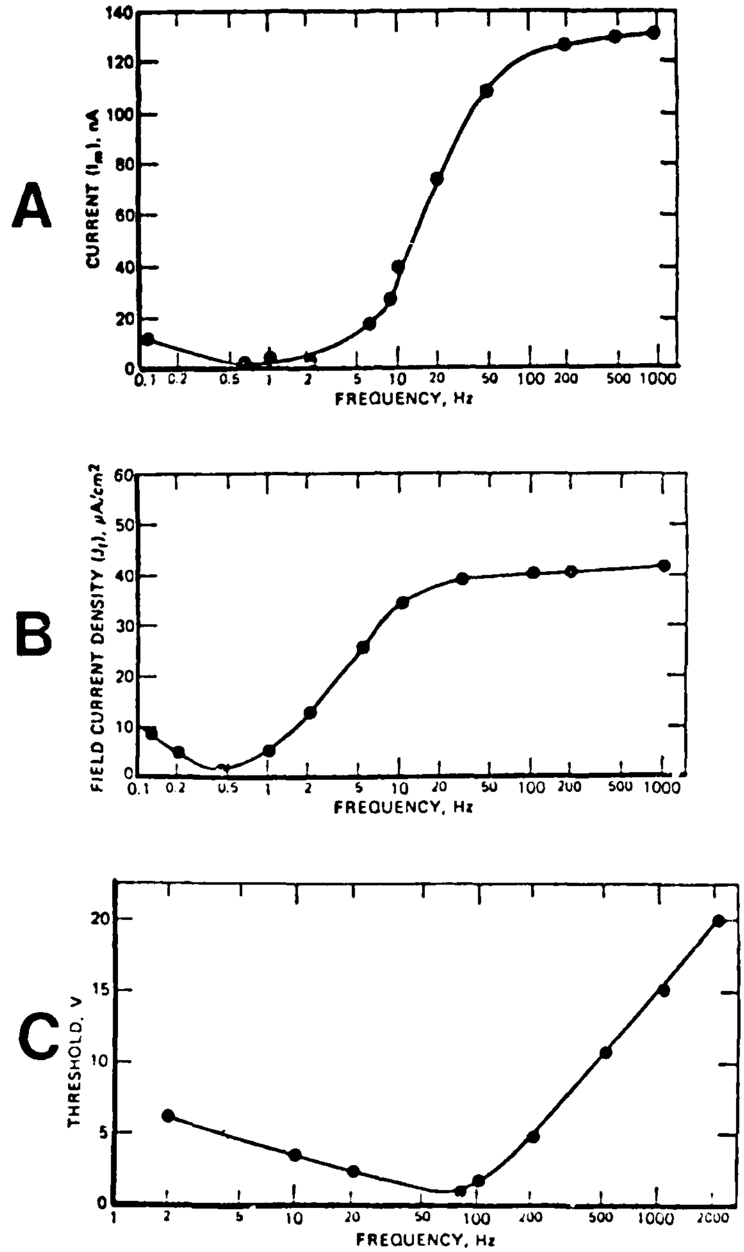

Figure 3. Plots of ELF thresholds needed to produce synchrony over a wide range of frequencies.

(A) For ELF currents which are injected intracellularly, i.e., through the microelectrode which also records the neuronal response.

(B) For ELF extracellular current densities which are established by passing current across the entire ganglion.

(C) For ELF signals, in the form of voltages which are applied to an electronic model of a mammalian pacemaker neuron.

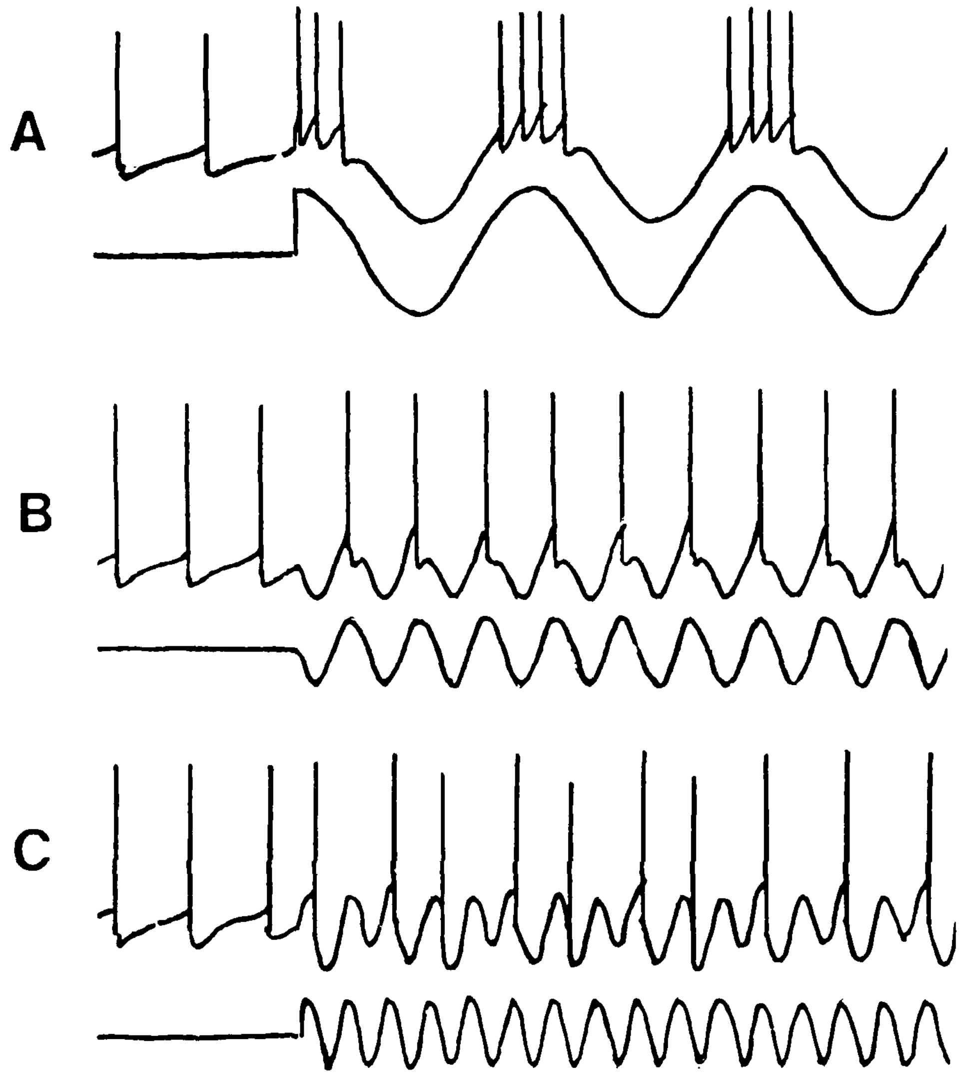

Figure 2: Examples of several modes of synchrony between an imposed ELF field and neuronal patterns. In each case the ELF current is shown below the transmembrane potential recording.

(A) For ELF frequencies well below FRo, several nerve impulses (spikes) are locked to each ELF half cycle.

(B) ELF frequencies slightly above FRo are effective in phase-locking the neuronal spikes on a one-for-one basis.

(C) For ELF frequencies several times greater than FRo phase-locking can take the form of spikes occuring on alternate cycles (e.g., 2-for-1 synchrony).

III. NEURAL EFFECTS OF ELF CURRENT DENSITIES BETWEEN 10^{-3} AND 10^{-6} A/cm^2

Generally speaking, TCDs in the A/cm^2 range cannot cause silent (i.e., resting) neurons to reach firing thresholds and thus do not produce "electric shock" types of responses. However, it has recently been demonstrated that relatively weak ELF currents (TCD between 10^{-3} and 10^{-6} A/cm^2) can appreciably modify the activity of nerve cells that are already firing--either due to endogenous pacemaker activity or other excitatory influences. Some examples of these neural activity modulations include the in vitro studies of synchronization of autorhythmic (i.e., pacemaker) neurons in the nervous system of the marine mollusc, <u>Aplysia</u> <u>californica</u>, and the rodent hippocampal slice.

The synchronization of <u>Aplysia</u> pacemakers by fairly weak ELF fields was reported by Wachtel (1979) and by Sheppard, French, and Adey (1980) using improved techniques. The state of synchrony achieved depends on the relationship between the ambient neuronal firing rate and the frequency of the applied ELF currents.

If the ELF field frequency is much lower than the ambient neuronal firing range then, at appropriate field strengths, synchrony is manifested by a "burst" patterning of firing wherein the <u>Aplysia</u> neuron will fire two or more spikes during the depolarizing half cycle of the ELF oscillation. For ELF frequencies close to the ambient firing rate, one-for-one synchrony is achieved. This phase-locking can be maintained for a large range of frequencies as long as the maximum firing rate of the neuron is not exceeded; however, for ELF frequencies that are multiples of the ambient firing rate, phase-locking is more readily achieved on a 2-for-1, 3-for-1, etc. basis between ELF frequency and captured neuronal firing rate. These various modes of phase-locking are illustrated in Figure 2.

The lowest thresholds we have seen are for the 1-for-1 lock-in (as illustrated in Figure 3b). In our earlier study (Wachtel 1979) we found that injected currents* on the order of 0.5 nA were often sufficient to produce phase-locking to an ELF frequency which was only slightly higher (less than 10) than the ambient neuronal firing rate (FRo). For ELF frequencies that are

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*The currents referred to in this section are injected via an intracellular microelectrode and the current density they engender cannot be directly measured. However, the TCDs that are equivalent in effects to these currents have been determined, as discussed on the next page.

crustacean stretch receptor, mammalian brain slice, etc.) have been used to confirm the notion that ELF fields giving rise to TCDs on the order of 1 mA/cm^2 achieve "shock" effects by virtue of depolarizing cell membranes by several mV and thereby cause nerve (or muscle) cells to fire directly (Kandel 1976).

It has been found that the frequency of a high level ELF current is not too critical for producing electric shock effects. Figure 1 shows that 60 Hz lies in the middle of a broad band of frequencies (from about 20 to 200 Hz) to which mammalian nerve or muscle cells are most sensitive. At lower frequencies the process of accommodation acts to limit sensitivity whereas at higher frequencies the membrane acts--due to its capacitance--as a low pass filter. The highly specific "frequency windows" that characterize reported responses to lower intensity ELF fields are not seen for these levels.

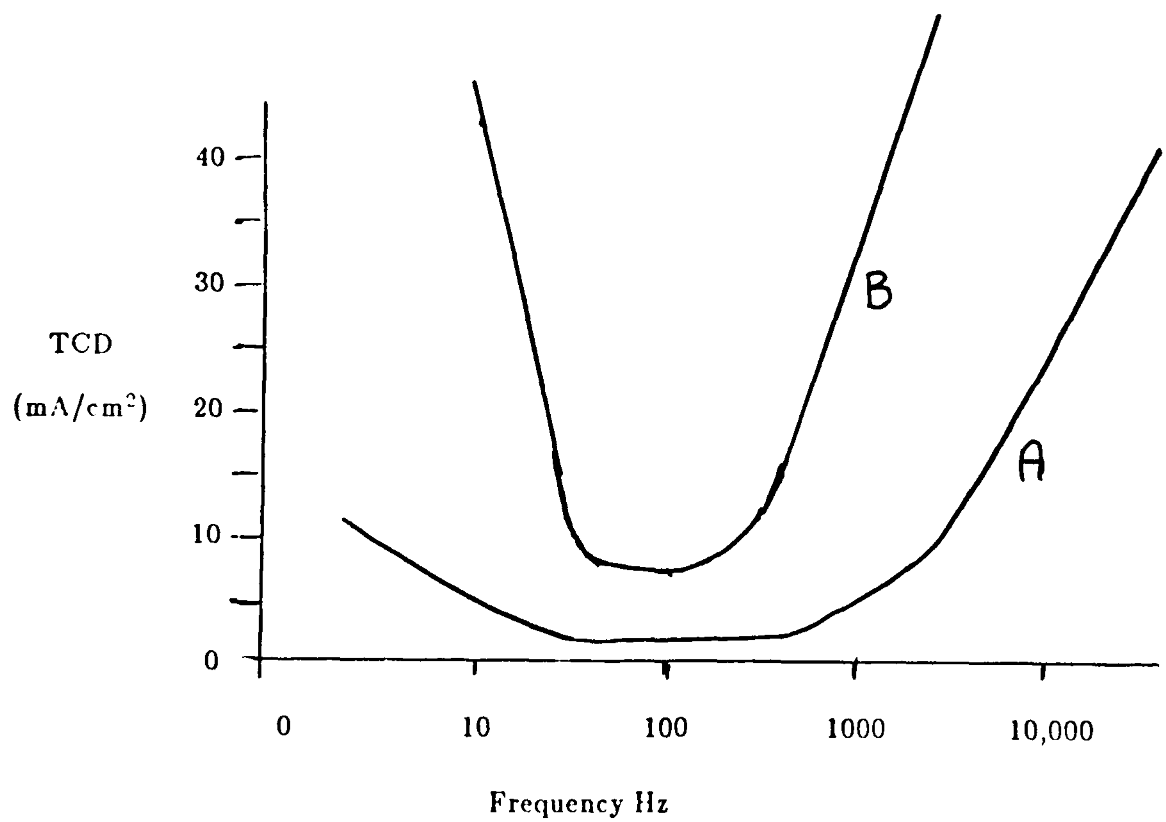

Figure 1. Threshold tissue current densities (TCD) needed to produce perception (Curve A) or "cannot-let-go" (Curve B) phenomena in human subjects. Adapted from work of Dalziel (1972).

summarizes these effects in humans. At 60 Hz, a total current of 1 mA applied to the fingertips can produce a noticeable sensation; approximately 10 mA (applied to the arms) will cause an involuntary skeletal muscle contraction leading to a "cannot-let-go" condition, and, most seriously, a 100-mA, 60-Hz current flowing from the arm can cause cardiac fibrillation (and thus death by electrocution). It is interesting to note that when these total currents are divided by the approximate area over which the current distributes itself, a TCD of about 1 mA/cm^2 results in each case. In other words, the heart is not 100 times less sensitive to ELF currents than sensory nerve endings (in the finger), but it is the wider distribution of the current over the torso which, fortunately, results in the seemingly higher threshold for cardiac disturbance by ELF currents. This factor was of major importance in understanding past cases of "microelectrocution". This unfortunate phenomena occurred as a result of small 60-Hz leakage currents, on the order of 10 μA, that entered the heart via indwelling catheters or implanted electrodes and were sufficiently concentrated to disrupt cardiac activity (Dalziel 1972). Approximating the area of these catheters or electrodes as 1.0 mm^2 again yields a figure of 1 mA/cm^2 as the effective tissue current density needed to produce cardial disturbance.

The whole issue regarding the "electrocution" level of ELF currents may appear to be irrelevant to the issue of weak ELF current effects except for one salient fact--the "microelectrocution" phenomena illustrates nicely the concept that it is the highly localized TCD that is of electrophysiological importance rather than total body currents.

This concept can be further delineated by relating "shock level" TCDs to transmembrane current densities (J_m) measured (usually) in various in vitro neural preparations. For example, in squid axon a J_m of 10^{-5} A/cm^2 will lead to a depolarization of about 10 to 30 mV and, thereby, cause the axon to fire (Hodgkin 1964). This J_m is only about 1% of the extracellular current density needed to stimulate the axon (or other neural tissue). However, it must be borne in mind that, at 60 Hz (or other ELF below about 300 Hz) the neural membrane has a high impedance relative to the surrounding fluid. Thus, about 99% of the extracellular ELF current will go around rather than through nerve cells. Schwan (1984) has quantified this "shunting effect" for loosely packed cell models and predicts the same approximate attenuation factor (100 to 1). A number of other in vitro preparations (e.g., Aplysia neurons,

For very intense ELF currents (TCD above $10^{-3}/cm^2$) the direct neural firing effects can be produced over a wide range of frequencies and amplitudes and doesn't seem to depend very much on "the internal state" of the neuron. Thus, there is virtually a certainty that these high currents will disrupt brain function under all conditions.

For weaker currents (TCD between 10^{-3} and 10^{-6} A/cm^2) certain perturbations of the neural firing pattern (such as phase-locking to an ELF current) can be demonstrated in vitro but only under fairly "special conditions"--namely, close proximity of ambient firing rates to the frequency of ELF currents and a restricted range of amplitudes. The likelihood of these conditions occurring over wide regions of the brain simultaneously is small, even though a "spreading zone of synchrony" effect is conceptually possible.

When the effects of very weak ELF currents (TCD below 10^{-6} A/cm^2) are examined it seems that the conditions for achieving an effect (such as "calcium efflux") are far more restricted to the narrow "window" ranges. The likelihood of these conditions occurring simultaneously and being widespread in the human brain is rather small. Consequently, the probability of these very weak ELF currents having significant effects on the intact human nervous system is also bound to be much smaller.

A varied array of experimental approaches, ranging from human volunteer subjects to isolated chick brains and molluscan neurons, have been employed in the history of exploring the effects of ELF fields on excitable cell function (i.e., nerve and muscle cells). A major problem in relating these studies to each other lies in making meaningful comparisons between the exposure conditions used. Based on our own work, as well as a survey of other approaches, it seems to me that the most rational way to compare the ELF dosimetry in various studies is to determine the tissue current density produced in each case.

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MAGNETIC AND ELECTROMAGNETIC FIELD EFFECTS ON BIOLOGICAL SYSTEMS

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INTRODUCTION

Increasing evidence from an ever enlarging data base of in vivo and in vitro studies using a wide range of approaches, state-of-the-art technologies, and closely monitored electromagnetic (EM) field exposure systems shows that there are at least some substantial effects of weak, extremely low magnetic and electromagnetic fields on biological systems. Studies of the interactions of magnetic and EM fields and organisms remain necessarily controversial with many essential questions unanswered and, in many cases, with essential questions not yet formulated. Magnetic and EM field studies have the potential to help one understand the fundamental basic biological processes such as how cell growth and replication can be controlled, how cells of the immune and the central nervous systems communicate, and how responses to other external stimuli can occur. However, inhibitory or stimulatory reactions during and following exposures to EM and magnetic fields have occurred under different experimental conditions, and, therefore, have often produced conflicting and confounding results and reports.

Indeed, the effects presented in the steadily increasing reports in the literature must be interpreted with caution. One reason is that most experiments were performed at only a few frequencies which were intermittently spaced across the EM spectrum. In the main, the frequencies of greatest experimental interest are those that have been allocated by the federal regulatory bodies to scientific, industrial, and medical uses and, hence, are the frequencies generated by readily available sources. Accordingly, a degree of risk exists in extrapolating results obtained at one frequency to untested frequencies. Furthermore, some experiments were performed on intact living animals (in vivo), while others were performed using laboratory preparations

(in vitro) of portions of organs, tissues, or cells in culture. However, effects on the intact living organisms are not always reflective of effects obtained in vitro and vice versa. In vitro experiments, in general, can provide closer control of parameters than experiments performed in vivo. Accordingly, results from in vitro studies may only assist in explaining effects observed during in vivo experimentation and, thereby, provide new directions for in vivo testing (Lerner 1984).

In addition, due to wide diversity in experimental models, frequencies, field strengths, and exposure system instrumentation and due to the difficulty in identically replicating experiments using unique techniques and technology, one can only speculate at the present time on whether the evidence from duplicated experiments and from different experiments that consistently reinforce each other will enable conclusions to be drawn as to any long-term significance associated with bioeffects associated with magnetic and EM field exposures. Since the extremely low frequency (ELF) fields do not have the energy to ionize or generate heat, it seems likely that the impact of weak magnetic and EM field effects would focus on the more subtle and indirect types of responses, thus making it more difficult to assess potentially beneficial or less desirable effects.

Questions about the measurement of EM field effects remain to be answered. Many experts have suggested that the commonly accepted measure, namely, power absorbed per unit mass as averaged over the entire animal, was not, by itself, an appropriate measure (Lerner 1984). As discussed by Wachtel (Wachtel, H. in Lerner 1984):

- EM fields can resonate with the overall size of the organism, as predicted by the antenna theory, and also with characteristic frequencies of oscillators present within the organism.
- Time dependence of the fields must be taken into account since duration of exposure may be as important as variation with time.
- With the accumulation of new data, the possibility increases that the critical factor may turn out to be the total absorbed energy, i.e., the power times the duration.
- Many effects do not steadily increase with increasing field amplitude but, instead, have "windows of effectiveness."

In this paper we have attempted to present and review the literature

relating to the possible biological effects or lack of effects of magnetic and electromagnetic fields. A majority of the reported literature centers on in vitro experiments using cells, microorganisms, and organ cultures; on in vivo experiments using animals; and on epidemiologic studies of workers and other persons advertently or inadvertently exposed to magnetic and EM fields. Accordingly, we have focused mainly on these types of biological studies with a consideration of additional types of studies as deemed appropriate.

IN VIVO STUDIES OF NONHUMAN BIOLOGICAL SYSTEMS

The effects of an EM environment on animal behavior, specifically on invertebrates, have been investigated in studies of the natural magnetic fields on the surface of the earth, as well as, in studies of artificial fields. Distinctions are usually made between experiments with magnetic fields that are generally static (Tenforde 1979) and experiments using EM fields established by induced electric currents.

Several genetic types of insects have been used as models in investigations using such study end points as orientation patterns, egg laying, and perception of gravity. In spite of earlier reports of contradictory results, the more detailed and better documented biomagnetic studies are providing increasing evidence that there are significant magnetic effects on such living organisms. The research reports of Mulay and Mulay (1964) and Close and Beischer (1962) indicating no genetic effect on organisms by altering a magnetic field have been contradicted by Levengood (1967). Levengood concluded that fly pupae subjected to magnetic fields exhibited morphogenetic anomalies that were transmitted for 30 generations.

Using _Drosophila melanogaster_ Turtox and Carolina Biological-CBS stocks of flies, Tegenkamp (1969) described the mutagenic effects of magnetic fields induced by permanent magnets. Magnetic fields of lesser or greater strength than that of the geomagnetic background induced mutations affecting the sex ratios of _Drosophila_. _Drosophila_, placed in a hypomagnetic environment (5.0-μT Helmholtz coil) after pairing, had highly significant increases in male offspring and in mutants that were without sex link inheritance, i.e., withered wings, convergent banding, and spotted abdomen. It appeared that only a few DNA synthesis fibrils were affected by the magnetic field as judged by the number of inbreeding generations before the occurrence of anomalies.

More recently, Ramirez et al. (1983) demonstrated that _Drosophila_ flies,

placed in a habitat with two lateral boxes, demonstrated sensitivity to magnetic fields such that oviposition decreased by exposure to pulsated ELFs of 100 Hz, 1.76 mT and sinusoidal fields (50 Hz, 1 mT). No initial effect of exposure to a static magnetic field of 4.5 mT was reported. Drosophila eggs treated for 48 h with the same fields showed that (1) mortality of eggs was lower in controls than in eggs exposed to all tested magnetic fields; (2) mortality of larvae increased when a permanent magnet was used; (3) mortality of pupae was highest when a permanent magnet was used; and (4) general adult viability was highest in controls (67%) and diminished progressively when eggs were exposed to pulsated (55%), sinusoidal (45%), and static (35%) magnetic fields. In their experiments, some lasting changes produced by ELF EM fields on Drosophila eggs at successive stages of larval and pupal development suggested possible teratological effects.

Structural modifications in the developing chicken embryo have been detected by Delgado et al. (1982) after ELF magnetic field (ELF-MF) exposures. Fertilized chicken eggs were incubated for 48 h while exposed to extremely low frequency magnetic fields of 10, 100, and 1,000 Hz with intensities of 0.12, 1.2 and 12 μT. Analysis of gross morphological and histological features of the exposed embryos showed that (1) ELF-MF of 100 Hz, 1.2 μT had the most consistent and powerful inhibitory effect on embryogenesis; (2) a window effect was demonstrated since embryos exposed to 100 Hz, 1.2 μT were less developed than embryos exposed at higher and lower intensities and frequencies; (3) developing organs reacted with different sensitivities to ELF-MF of specific frequencies and intensities. For example, the cephalic nervous system was the most sensitive, and the heart was the least sensitive, while somites were not disturbed by exposure to 10 Hz with any of the intensities used. And (4), the marked embryological disturbances described were attained with much lower intensities, namely 0.01 G, than those used in studies by other investigators. In subsequent work, Delgado and coworkers (Ubeda et al. 1983) examined the importance of waveform in determining the biological response of the developing embryo. In these experiments freshly fertilized hen eggs were exposed to 100 Hz with a pulse width of 500 μs. Four different pulse shapes were used, and magnetic field intensity varied from 0.4 to 104 μT. Although a number of previous studies have suggested that the waveform may be very important in induction of biological effects using coupled electric or magnetic fields, increasing

evidence suggests that the shape of the applied wave may not be as important as the pulse characteristics, such as frequency and rise time (Rozzell 1984). Studies showing osteogenesis to be highly dependent upon the waveform of the applied field have been reported by Pilla (1974) and Bassett (1982).

The developing chick embryo is apparently very sensitive to extremely low frequency, extremely weak magnetic fields. A number of additional observations by Delgado and coworkers have suggested that placement and orientation of the egg with respect to the earth's magnetic field appears to be very critical to the effects observed. When magnetic field treated eggs were opened at the end of the 48-h incubation period, embryos were observed to have changed position in the egg and to lie approximately perpendicular to the long axis. Almost all of the embryos that did not reorient themselves and hence remained parallel to the direction of the magnetic field were abnormal. None of the control embryos changed position during the 48-h incubation period (Rozzell 1984).

Using low intensity magnetic fields, Persinger and Coderre (1978) studied thymus mast cell (MC) numbers in 200-day-old rats following perinatal and adult exposures to 0.5-Hz rotating magnetic fields. Rats that had been exposed from 2.5 days before to 2.5 days after birth to either 0.5-Hz rotating magnetic fields between 10^{-3} T to 10^{-8} T or to sham fields were maintained after weaning in one of two typical caging conditions. These animals were then reexposed as adults to one of three intensities (10^{-6}, 10^{-7}, or 10^{-8} T), to sham fields, or to colony room control conditions. Perinatally exposed thymuses from adult rats displayed a marginally significant (i.e., 20% to 35%) elevation in mast cell numbers relative to sham field controls. However, the adult exposures did not significantly effect the mast cell numbers. The two post weaning caging conditions, a nonmagnetic and variable magnetic field, induced a significant (35%) difference in MC numbers. Accordingly, the absence of significant perinatal and adult interactions with rotating magnetic field exposures indicated that early magnetic field exposure did not alter adult thymus responses to weaker, but more natural, intensity levels. One interesting feature of the perinatal rotating magnetic field effect, despite the large statistical overlap with sham-field controls, involved the apparent long-term expression of the change. Thymic mast cell differences were still found in 200-day-old exposed rats, despite varying post weaning treatments. Whether these differences reflected actual long term and

chronic elevations in thymic mast cell numbers or the enhanced tendency for perinatal rotating magnetic field exposed rats to increase thymic mast cell numbers following small environmental changes is not clear. Unlike the caging effects, the perinatal rotating magnetic field exposed rats displayed no gross changes in body weight, but they had significant changes in both relative and absolute thymus and testicle weights, as well as significant decreases in serum glutamate oxaloacetic transaminase activity, lactate dehydrogenase activity, and blood urea nitrogen levels.

In a companion paper, Persinger et al. (1978) presented additional information about the rats exposed perinatally and as adults to 0.5-Hz magnetic fields. Of the 36 blood, tissue, and consumptive measures evaluated, rats exposed perinatally to rotating magnetic fields displayed significant (20) reductions in urea, GOT, and LDH activities, 4 increases in testicle weights, and 17 decreases in thymus weights relative to perinatal sham field controls. The absence of significant perinatal condition verses adult-condition interactions did not support the hypothesis that perinatal rotating magnetic field exposure might enhance responsiveness to more natural, less intensive field variations.

In in vivo studies of *A/J female mice by Batkin and Tabrah* (1977), the exposure of the A/J animals bearing transplanted neuroblastoma cells to a 12-G, 60-Hz magnetic field for 16 days, starting 3 days post transplant, resulted in an early slowing of tumor growth, more free red blood cells in the tumor areas, and a tendency to focal tumor cell destruction, thus suggesting that a small alternating magnetic field may effect transplanted tumor growth. In a follow-up study, Batkin, Guernsey, and Tabrah (1978) detected changes in cell sodium pump activity following whole animal exposure to weak AC magnetic fields. In this biological system, the cell membrane enzyme ((Na^+ - K^+) - ATPase) responses were measured following exposure of the tumor-bearing and normal animals to a weak AC magnetic field of 55 to 60 G, 60 Hz. Analysis of sodium pump activity in normal mouse tissue revealed that the kidney cortex and diaphragm showed a significant reduction in enzyme activity as did liver tissue after 11 days of exposure to the magnetic field, but at day 17 the levels had returned to control values. In mice bearing transplanted neuroblastoma cells, a reduction in the Na^+ - K^+ - ATPase activity was also revealed, and this persisted at day 17.

Biological effects of a 60-Hz magnetic field (0.11 T) on mice were also

reported by Fam (1981). Results of this investigation clearly indicated that mice exposed to alternating magnetic fields consumed more drinking water than their controls, and the consumption per gram of body weight was 37% higher in the exposed mice. During the exposure period, exposed animals lost weight compared with a control group, and, on the average, the growth of the exposed mice, as measured by body weight, was retarded by 8.53%. On the other hand, no statistically significant effects were found in the blood count, white cell differential count, or blood proteins of the exposed mice as compared with control mice. Moreover, long term exposure studies did not reveal any harmful effect on the reproductive ability of the mice after continuous exposure to the field, nor were there significant differences in the number of born or surviving progenies or the average weight per progeny between the exposed and control animals. Histological studies of the main organs of the exposed mice did not reveal any abnormal pathology.

Schober, Yanik, and Fischer (1982) used female white mice to test the influence of weak magnetic fields on their electrolyte balance. These investigators used three types of magnetic fields, namely 50-Hz sinusoidal, and 10- and 50-Hz rectangular fields. The 50-Hz sinusoidal and rectangular fields induced no significant changes in the animals' electrolyte balance. However, calcium levels were significantly lower in test animals than in controls at both times studied, i.e., 1 and 7 days of exposure. A one day exposure to a 10-Hz rectangular field significantly lowered sodium and increased potassium levels. These results were almost reversed after 7 days of recovery. The magnetic field strength in all exposures was 10 G.

In other studies of in vivo effects, Udintsev, Serebrov, and Tsyrov (1978) studied albino rats exposed to a variable magnetic field with an intensity of 200 Oe of industrial frequency for different durations and at different intervals while measuring the uptake of ^{131}I by the thyroid gland, of thyroxine, and of protein bound iodine (PBI) concentration in blood plasma. PBI levels rose after 15 min of exposure. With an increase in the exposure time to 6.5 h and, in particular, to 24 h the PBI level and thyroxine uptake fell. Repeated exposures to variable magnetic fields (up to 6.5 h daily for 5 days) resulted in a significant increase in ^{131}I concentration in the thyroid gland and in PBI levels, whereas, thyroxine uptake by the tissues was considerably reduced. The authors suggested that the state of the thyroid function and tissue response to thyroxine were modified depending on the

duration and rhythm of exposure to the magnetic field.

Barnothy (1964) reported that the growth of transplanted tumors in mice could be influenced by strong static 2,400 to 4,500 Oe magnetic fields using permanent magnets. The results of several experiments using T-2146 adenocarcinoma cells as the transplanted tumor showed growth in all hosts. The effect of the magnetic field was to arrest tumor growth, followed, not by subsequent size diminution, but by an abrupt rejection of the tumor. After a second series of experiments, using mice inoculated from a homotransplant of the first experiment and reexposed to magnetic fields produced by the DuBois magnets, the tentative results indicated that rejection of tumor could be expected only in a first homotransplant but not in subsequent homotransplants. In follow-up studies, using isotransplants, and C3HBA mammary gland carcinoma cells, none of the magnetic field treated mice rejected the tumor, but their average life span after transplantation was 35% longer than that of the controls. Overall, investigations suggested that in fields of 2,400 to 4,500 Oe and of not less than 1 MOe^2/cm paramagnetic strength, a rejection of homotransplants can be achieved in 20 to 80 percent of cases with a probability level of 1:1000. A rejection of isotransplants was observed only in fields with more than 5 MOe^2/cm paramagnetic strength. In fields of 4,200 Oe with 0.12 MOe^2/cm paramagnetic strength, a lengthening of the life span of mice with isotransplants was observed with a probability level of 1:500.

One additional area of long-term investigations of magnetic field effects involves pulsed magnetic fields and the repair and healing processes associated with fractured and diseased skeletal system elements (Bassett, Pawluk, and Pilla 1974; De Haas, Lazarovici, and Morrison 1979). The effects of pulsating magnetic field (50 G, 50 Hz) generated by a therapeutic device on growth of Ehrlich ascites tumor cells in vivo and on cellular respiration in vitro have been studied by Zecca and Dal Conte (1983). Their preliminary report suggested, most significantly, that oxygen consumption for exposed and control cells did not change, nor was survival for most exposed tumor-cell injected animals significantly extended over nonexposed controls. Survival of one exposure group was extended over controls when the animals were exposed to magnetic fields 7 days before and 7 days after i.p. injection of tumor cells. Most recently, Ottani et al. (1984) detected significantly increased ornithine decarboxylase and DNA synthesis in rat liver after partial hepatectomy and

exposure to pulsed 50-Hz, 6-mT to 400-Hz, 0.6-mT mixed electromagnetic fields, thus, indicating an enhanced rate of regeneration and recovery.

IN VIVO HUMAN STUDIES

Investigations of the effects of 50- and 60-Hz magnetic fields on humans have not been described in very many research reports. No mechanisms are presently known whereby magnetic fields could produce effects on intact human biological systems, aside from the production of eddy currents. It is known that very strong fields, those of 10 mT and above, cause flashes of light to be seen by people whose heads are exposed. These phenomena are called "magnetic phosphenes," but the mechanism by which they are produced is not well understood. Low intensity magnetic fields are not apparently perceived by humans. Although general symptoms and functional disorders have been attributed to magnetic field exposures, for the most part, they can be explained in other ways. Rigorous evaluation of the results of prior studies has been lacking, and the data collected up to the present time suggest that much of what has been reported could be due to multiple influences. Information about reaction times and other psychophysiological parameters should be treated with appropriate caution, since no direct pathological reactions have been reported (Hauf 1982).

Only a few studies have directed their attention to the combined effects of well defined electric and magnetic fields on humans. In general, epidemiological studies of electric fields have regarded the magnetic field effects as unimportant. The increasing body of evidence suggesting a possibility of magnetic field effects awaits confirmation. Results from the studies that have been performed suggest that the combined electric and magnetic fields may have either an inhibitory or an enhancing effect depending upon which of several physiologic and hematologic parameters were studied. Overall, the experiments which have been performed leave open the possibility that the results may be the consequence of different experimental conditions, including different exposure parameters (Hauf 1982). Hauf has not observed any illness resulting from the influence of magnetic fields (some of which exceeded 10 mT and to which workers were exposed for up to 8 h/day) during approximately 30 years of examinations of workers in the electrical and electrochemical industries (Hauf 1982). Reviews of studies have shown that electric fields of intensity of up to 20 kV/m and magnetic fields of intensity

p to 240 A/m (0.3 μT = 3 G) do not constitute a detectable danger to health Miller 1983).

Addressing the possibility that EM and magnetic fields could be associated ith carcinogenesis, proliferative changes, and genetic alterations, several tudies have presented conflicting evidence, mostly of an epidemiologic ature. At the present time, the majority of published evidence leans towards he possibility of some type of linkage between human cancer and exposures to M, electric, and magnetic fields. In 1979, Wertheimer and Leeper reported he results of their study of electrical wiring configurations and childhood ancer. They found an excess of electric wiring configurations suggestive of igh current flow in homes of children who developed cancer as compared to hose of control children. This finding was strongest for children who had pent their entire lives at the same address; it appeared to be dose related; nd it did not seem to be an artifact of neighborhood, street congestion, ocial class, or family structure. These authors suggested that if magnetic ield exposures were responsible for their findings, duration of continuous xposure above some minimum threshold would be more important than strength of xposure per se. Indeed, prolonged exposure to the magnetic fields within a 001 -.1 G range most pertinent to wiring effects has not been explored xperimentally. Previous experiments have been conducted using fields onsiderably higher (.5 to 30 G) than the 60-Hz fields generally found near ower lines. Results from these prior studies often appeared to be unrelated o dose over the ranges studied. Wertheimer and Leeper also suggested several ossibilities for consideration as to how residences near a high current onfiguration (HCC) of electrical wiring might effect the development of ancer. Among these possibilities were that magnetic fields produced by wire urrents may somehow directly cause cancer, that carcinogenic activity may be ssociated with some indirect effect of the HCCs, and that AC magnetic fields ight affect the development of cancer indirectly through some effect on the hysiologic processes. For example, they suggested that contact inhibition of ellular growth or the basic immune reaction of recognizing "self" from "not elf" involves electrical potentials occurring at cell surfaces. These uthors emphasized that although the risk of cancer appears to be increased or children living near HCCs, it is rarely increased by a factor of more than wo or three. Accordingly, the practical significance of the correlation, if ny, lies in the high prevalence of HCCs, not in any very high risk posed by

HCCs (Wertheimer and Leeper 1979).

ulton et al. (1980) repeated essentially the same type of study in Rhode d as that conducted in the greater Denver, Colorado area by Wertheimer Leeper (1979). In contrast to Wertheimer and Leeper's results, no ionship was found between leukemia and electric power line gurations. The Fulton et al. results pointed toward the conclusion that ıch a relationship exists for the population studied, it must be very . If the relationship found in the greater Denver area was real it may been the result of an interaction between magnetic fields and some other r which is stronger in the greater Denver area than in Rhode Island.

critique of the Wertheimer and Leeper study by Miller (1980) pointed out a dose response relationship was suggested in their study, but no doses , magnetic field intensities) for any addresses were given. Moreover, r (1980) provided evidence that a household magnetic field from rical appliances found in the home would exceed by far any magnetic ls resulting from electrical wiring configurations in the environment de the home. A recent Swedish study by Tomenius, Hellstrom, and Enander) of 716 cases of childhood cancer confirmed the findings of Wertheimer eeper (1979) concerning dwellings with a visible 200-kV high tension line n 150 m from the homes and concerning dwellings with a measured magnetic l of 0.3 μT or more.

or approximately two years the conflicting reports of Fulton et al.) and Wertheimer and Leeper (1979) appeared to essentially neutralize other, and, in the minds of the general scientific population, neutralize ssue. Then, in 1982, Wertheimer and Leeper reported that, like childhood r, adult cancer was found to be associated with high current ele rical g configurations near a patient's residence. Several patterns in their ted data suggested that HCCs and cancer may be causally linked. For le, a dose relationship was found which did not appear to be an artifact e, neighborhood, or social economic level. The association was most ly demonstrable where cancer caused by urban-industrial factors did not e the effect. A distinct pattern of latency between the first exposure and cancer diagnosis was seen. This was consistent with a hypothesis ncer stimulation produced by alternating magnetic field exposures.

ur recent reports (Coleman, Bell, and Skeet 1983; McDowall 1983; Milham , Wright, Peters, and Mack 1982) also suggested an increased risk of

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conflicting and controversial since they usually did not include sufficient details about experimental conditions to obviate doubts about possible effects of environmental and other confounding factors.

- Fourth, results from in vivo studies of biological effects of magnetic and EM fields indicate that such fields can affect insect behavior as well as induce increased mortality and mutagenic effects under special experimental conditions. Magnetic fields of specific frequencies and intensities have been shown to inhibit chicken embryogenesis with specific organ sensitivities.

- Fifth, increasing evidence supports the role of EM and magnetic fields as mediators in special cell systems for interactions of Ca^{++} ions as well as for hormone-receptor and receptor-enzyme coupling at cell membranes.

- Sixth, exposures to ELF EM and magnetic fields have been shown in several laboratories worldwide to stimulate nerve and glial cells in nerve tissue.

- Seventh, increasing evidence from several in vitro approaches investigating bioeffects of magnetic and EM fields shows that specific modulation of normal cell functions, including effects on cell respiration and growth rates, mitotic cycle effects, DNA synthesis, enzyme activities, and transcription induction, consistently occur during and following exposure to EM and magnetic fields of specific intensities and durations.

- Eighth, when viewed overall, one can conclude that there are numerous well described studies which present valid results indicating significant effects on basic biological systems and interactions caused by or as a result of exposure to magnetic or EM fields. Accordingly, these reports fall into several basic areas (i.e., cell communication, reproduction, and survival) and justify continued research to help answer the final questions about affects and effects of magnetic and EM field exposures as they relate to possible risks, benefits, and harm.

- Ninth, the only certain biological effects of ELF magnetic fields are the magnetophosphenes, which are sensations of light flashes in the eye caused by magnetic flux densities up to 40 mT within the 40 to 45-mT frequency range.

embryogenesis and organ sensitivity to magnetic fields of specific frequencies and intensities have been shown by Delgado and coworkers (Delgado et al. 1982; Ubeda et al. 1983), while EM and magnetic field effects on hormone and enzyme activities and DNA-translation have been described by Aarholt, Flinn, and Smith (1982), Batkin, Guernsey, and Tabrah (1978), Goodman, Bassett, and Henderson (1983), Liboff et al. (1984), Ottaini et al. (1984), Udinstev, Serebrov, and Tsyrov (1978). If there are covert mechanisms regulating the basic biological processes sensitive to the effects of magnetic or EM fields, at present, no one understands them sufficiently. Therefore, it seems likely that continued research should provide an answer relatively soon as to whether or not there are significant effects of magnetic or EM fields on biological models and whether the detected affects or effects are useful in assessments of risk, benefit and less desirable states.

CONCLUSIONS

Our conclusions reflect our evaluations of past and current information about studies of changes, or lack of changes, in biological model systems during and after exposure to magnetic or electromagnetic fields, particularly those of extremely low frequency. Information was derived from the open international literature available primarily from computer data bases and from reference lists, translation services, institutes, and individual scientists.

- First, very little information is available regarding any newly proposed basic principles or mechanisms of action between ELF magnetic or EM fields and living organisms.

- Second, results from most investigations of bioeffects of ELF magnetic or EM fields reported earlier, prior to about 1980, did not provide sufficient experimental information about intensity and duration of exposure, experimental conditions, and statistical analysis of the results to enable evaluations to be made. In contrast, investigations of bioeffects of ELF magnetic or EM fields reported more recently, i.e., within the last four years, have provided in the main, increasingly detailed information about exposure conditions and systems, biological models used, and how results were analyzed. However, there remains a need for standardized methods for describing--in formatted detail--all essential experimental information and EM fields so that comparisons of results from individual reports can be easily performed.

- Third, results from most of the earlier in vivo and in vitro investigations of bioeffects of magnetic or EM fields are

Accordingly, the degree of change should be in comparison to changes from other variables that are incorporated within the experimental design such that some reference can be used to determine an absolute magnitude of magnetic or EM effect (Persinger et al. 1978). Indeed, a common error has been to confuse correlation of a change observed subsequent to exposure to EM fields with causality, attributing change to the direct action of the EM field (Foster, K. R. in Lerner 1984).

The relatively small magnitude of the in vivo and in vitro effects described so far strongly suggests that a particularly close look be given to experimental techniques employed. Moreover, carefully documented monitoring of all external and internal parameters of the test systems, including the environment of exposure, the biological model system, and the instrumentation used in generating the fields and in their monitoring, should be achieved. The magnetic and electromagnetic fields used should be characterized as completely as possible, and appropriate biological and EM exposure system controls should always be concurrently run with each experiment as time, space, and experimental design permit.

The large numbers of reports showing no effects in several well studied cellular and subcellular systems suggest that magnetic and EM fields may turn out to have specific interactions with a limited number of biological structures, processes, or states, and only through these interactions can magnetic and EM fields induce changes of biological significance.

Accordingly, new "indicator" systems are needed to supplement the classical approaches in studies of simple model systems of biologically important molecules, cellular and subcellular structures, and tissue and organ structures in order to detect subtle and perhaps not yet recognized effects of magnetic and EM fields.

Recent reports have observed modulation of normal cell functions and processes by EM or magnetic field by using activators or inhibitors to enhance the detection of subtle field induced effects in several biological models (Aarholt, Flinn, and Smith 1982; Chiabrera, Grattarola, and Viviani 1984; Chiabrera et al. 1983; Colacicco and Pilla 1983; Conti et al. 1983; Luben et al. 1982; Norton 1982; Piruzyan and Kuznetsov 1983).

More direct effects of magnetic or EM fields have been reported by Tegenkamp (1979) and Ramirez et al. (1983). This includes mutagenic effects and increased mortality in the Drosophila model. Inhibition of chicken

in the control culture; exposed cells underwent DNA synthesis more rapidly. They believe that one can influence individual mechanisms of specific activities through the quantum biochemical interaction mechanism from the possible universal interaction of a magnetic field with a biological substrate. On the other hand, Piruzyan and Kuznetsov (1983) suggested that magnetic fields can rarely act on biological systems in view of their studies and reviews of studies showing negative effects in a wide variety of model systems. Constant magnetic fields were demonstrated to have effects on skin respiration, and on nerve and glial cell reactions, while variable magnetic fields induced changes in Ca^{++} concentrations intracellularly and in its transport through cell membranes.

SUMMARY

A possible biological action of constant and variable magnetic fields have stimulated large numbers of research publications in recent years. Unfortunately, much of the research has been performed using inadequate apparatus and techniques, and the information given in these reports often has been contradictory and unconvincing. Accordingly, reliable conclusions regarding the formulation and testing of basic principles of interaction, action, or reaction of magnetic fields in these biosystems cannot be derived. Indeed, the very existence of significant magnetic-induced biological effects remains a subject of continuing controversy. In view of the importance of possible magnetic and EM field effects on biological systems, the demonstration of reproducible significant effects in a model system, the complete description of the experimental conditions which permitted their detection, and the formulation of mechanisms upon which the observed effects could be based will help to enhance our knowledge about the underlying nature of some of our most basic biological interactions and processes.

In surveying and evaluating the current literature, an obvious paucity of information exists about the intensity and duration of exposure, the experimental conditions, and the statistical analysis of the results (Waskaas 1981). Even when there is detection of statistically significant changes in the target organismic system, it is important to evaluate the results carefully. A point forgotten by some reviewers and researchers alike is that statistical significance does not necessarily determine practical significance and may only reflect the sophistication of the measurement procedures.

and immune systems of animals has been well established. More recently, work in the field has been directed towards constructing a framework for explaining these effects. Previous research has indicated that calcium (Ca^{++}) ions play a critical role in helping to control electrical impulses generated at the nerve cell membranes and that these pulses are important in transmitting information in the nervous system. Work in this area by Adey and his colleagues showed that changes in Ca^{++} effects could be produced by extremely low frequency fields at field strengths of a microvolt per centimeter, a finding that has developed into one of the most solid indications that athermal effects exist. With the increasing duplication of these results in other laboratories, it is increasingly evident that cell membranes and Ca^{++} transport linked to weak ELF EM fields may be the key to some biological effects (Piruzyan and Kuznetsov 1983).

Geomagnetic effects have recently been suggested as having important influences on biological effects of extremely weak pulsed magnetic fields. Blackman et al. (1984) recently reported testing the hypothesis that enhanced Ca^{++} efflux from chick brain tissue in vitro was due to the magnetic field component. Similar geomagnetic field influences have been suggested by Delgado et al. (1982) and by Liboff et al. (1984).

In a summary article, Toroptsev and Taranov (1982) suggested that the effect of magnetic fields on living systems does not evoke any doubts that a high sensitivity of various biological subjects to fields can be demonstrated. These authors feel that a higher biological activity of alternating and, especially, pulse magnetic fields, as compared with constant magnetic fields, has been shown and that numerous biotopic parameters of magnetic fields have been clarified including the field's intensity, its gradient, sense of the vector, and exposition. They suggest that the parametric differences of magnetic fields form the basis of their varying biological activity since the biological effect can be caused primarily, in one case, by the intensity of the magnetic field and, in another, by its space-time characteristic. The nature of the response of cultured cells to magnetic fields depends on their functional state. Accordingly, the effect of a pulsed electromagnetic field on chick embryo fibroblast culture cells at different phases in the chick's development gives different and even opposite results. In cultures at log growth phase under the effect of a pulsed electromagnetic field, the duration of the mitotic cycle was 4 h shorter than

salmonella mutant strains were observed between exposed and nonexposed cultures, although 150 G stimulated growth of these two strains, while 300 G was inhibitory.

More recently, Ramon, Ayaz, and Streeter (1981) described inhibition of the growth rate of E. coli as induced by 60 h of ELF weak magnetic fields, i.e., 60- or 600-Hz magnetic field of strength, 2×10^{-3} T. Cell wall rupture was also described. Also using E. coli, Aarholt, Flinn, and Smith (1981) detected significant effects of low frequency magnetic fields, specifically the mean generation time (MGT) was reduced at a peak 50-Hz field strength of 4.8 G and rose again at approximately 8 G. At 16.66 Hz a similar decrease was observed at 800 mT. A strong threshold effect was observed as were strong indications of periodicity of MGT against magnetic field strength. It was suggested that some quantum-mechanical effect was involved. These investigators subsequently extended their studies into the magnetic field effects on the lac operon system (Aarholt, Flinn, and Smith 1982). A very strong dependence of the rate of β-galactosidase synthesis on field strength was seen with a decrease in synthesis beginning at 0.27 mT, returning to control values at 0.32 mT, and then an increasing rate of synthesis at about 0.54 mT. The authors suggested that very critical values of applied magnetic field can have significant effects at the DNA-RNA level, since β-galactoside synthesis is directly controlled by the presence or absence of the repressor protein on the DNA chain.

Luben et al. (1982) detected inhibition of responses to parathyroid hormone and osteoclast activating factor in cultures of osteoblast-like mouse bone cell line MMB-1 exposed to two EM fields, one of continuous pulse trains (72 Hz) and the other of recurrent bursts (15 Hz) of shorter pulses. The field effects were suggested as being mediated primarily at the plasma membrane of osteoblasts by interrupting hormone-receptor interactions or receptor-cyclase coupling in the membrane. Recently, Jolly et al. (1983) used isolated rabbit islets of Langerhans to demonstrate magnetic field effects on Ca^{++} efflux and insulin secretion. Exposure of the cells to a low frequency pulsed magnetic field (4 kHz, 20 to 30 G), as described by Luben et al. (1982), for 18 h 37°C resulted in a reduction of 26% in $^{45}Ca^{++}$ content, 25 in $^{45}Ca^{++}$ efflux, and 35% in insulin released during glucose stimulation when compared with appropriate controls.

Within the last ten years, evidence of EM effects on the nervous system

two-phase aqueous polymer system than control cultures. These results suggest that exposure to the EM fields induced a variation in cell surface membrane charge or alterations in the distribution of cells among cell cycle stages. In other studies, Greenebaum, Goodman, and Marron (1982) reported that P. polycephalum exposed to 2.0-G, 75-Hz magnetic fields displayed a longer mitotic cycle than nonexposed control cultures. In 1979, Greenebaum, Goodman, and Marron described significant changes in several biological parameters observed during continuous exposure to ELF EM fields for periods varying from 2 months to 5 years. Cultures were exposed to 45-, 60-, and 75-Hz CW and 76-Hz frequency modulated fields with electric field intensities varying from 0.04 to 0.7 V/m^{-1} RMS and magnetic fields from 0.01 to 0.2 mT. The biological changes observed were generally those associated with a slowing down of cellular processes, e.g., a longer nuclear-division cycle and depressed respiration rate were seen under exposure to most CW and all frequency modulated fields tested. These investigators also reported (Goodman, Greenebaum, and Marron 1979) bioeffects of ELF EM fields observed in their studies of P. polycephalum during prolonged exposure to either continuous wave (75 Hz) or frequency modulated wave (76 Hz) EM fields (0.1 to 2.0 G and 0.035 to 0.7 V/m). Both exposure conditions were found to lengthen the mitotic cycle and depress respiration rates. Once established, the effects persisted indefinitely in the presence of EM fields. Similar effects were observed when either individual electric fields (0.7 V/m) or magnetic fields (2.0 G) were applied. For magnetic fields indirect evidence suggested that threshold levels were below 0.4 G.

The effect of in field exposures to magnetic fields on mutation rates and growth of the bacterium E. coli and the fungus Pencillium chrysogenum was investigated by Riviere (1976) using magnetic fields (50 Hz) of 10 to 350 G. Neither mutation nor growth rate changed during 48-h exposures. Subsequently Moore (1979) grew five bacteria and one yeast in magnetic fields of 50 to 900 G with frequencies of 0 to 0.3 Hz and square, triangular, or sine wave forms. A somewhat greater stimulatory growth response to the magnetic field was shown by two gram negative bacteria than by two gram positive bacteria or the yeast. Maximum stimulation of growth occurred at 150 G and 0.3 Hz, and maximum inhibition occurred at 300 G. Growth curves were similar for each of the three wave forms tested at 0.3 Hz and field strengths of 50, 150, 300, and 600 G. No differences in spontaneous mutation frequency or revertants of two

markedly reduced at all four frequencies, ConA was reduced at 3 and 50 Hz, and PWM was significantly affected only at 3 Hz. The authors suggested that an alteration of calcium fluxes by EM fields could explain the observed inhibitory effect on human lymphocyte blastogenesis. Using 60-Hz EM fields, Livingston et al. (1984) exposed human lymphocytes from 14 donors for 68 h to a variable electric fields (0.003, 0.03, 0.3, and 3.0 mA/cm^2) and a constant magnetic field intensity (2.0 G) and exposed CHO cells to 0.03 mA/cm^2, 2 G for 26 h. Preliminary results showed no field effects were shown as measured by sister chromatid exchange, frequency and replication indexes of lymphocytes and analysis of micronucleus in exposed CHO cells.

Chiabrera and coworkers have attempted to model the perturbations induced by low frequency EM fields on membrane receptors of stimulated human lymphocytes (Chiabrera, Grattarola, and Viviani 1984; Chiabrera et al. 1982; Grattarola, Viviani, and Chaibrera 1982). Grattarola, Viviani, and Chaibrera (1982) described their modeling in terms of the fields on the system's free energy. Subsequently, Chiabera, Grattarola, and Viviani (1984) proposed possible mechanisms to help understand the aggregation between lectins and lymphocyte surface receptors that can be strongly affected by a low level electric field induced in a cell suspension by a time varying magnetic field. These investigators suggested that microelectrophoretic effects on ligands and surface receptors can offer an explanation for interactions between ELF fields and cells in this and in other biological systems.

Recently, Goodman, Bassett, and Henderson (1983) compared repetitive single pulse and repetitive pulse train EM fields by monitoring transcription in dipteran salivary gland cells by tritiated uridine, autoradiography, cytological nick translation, and analysis of isolated RNA fractions. The single pulse (0.05 G) increased the messenger RNA specific activity after 15 and 45 min of exposure, while pulse train (0.1 G) increased this activity only after 45 min of exposure. These results suggest that pulsed EM fields induce specific modifications in normal cell function and that one effect can be related to transcriptional induction.

In addition, Marron et al. (1983) studied an amoebae, P. polycephalum, grown in liquid medium and exposed simultaneously to a 60-Hz sinusoidal field of 1.0 V/m and a 60-Hz sinusoidal field of 0.1 mT applied perpendicular to each other in the plane parallel to the earth and in phase with one another. Exposed cells were observed to have a smaller partition coefficient in a

20 h) and DNA synthesis. The range of magnetic field amplitudes tested encompassed the geomagnetic field suggesting that mutagenic interactions could possibly arise from short-term changes in the earth's field. Liboff and Kaplow (1984) recently reviewed the evidence linking leukemia to EM radiation exposure and discussed reports showing low frequency time-varying magnetic field effects on various biological mechanisms from DNA synthesis to embryonic development to mRNA transcription.

Preliminary results from recent investigations using well recognized human cancer cells from continuous cultures have suggested that continuous 24-h exposures to 60-Hz magnetic fields (1.0 G RMS) alone and in combination with 60 Hz electric fields (300 mA/m^2 current density RMS) could enhance human tumor cell proliferation as measured by cloning in agar growth assays (Winters and Phillips 1984a). These data indicate that single exposures of human tumor cells to EM fields produced a long term change in the ability of the target cancer cells to reproduce and that a major component in producing this effect appeared to be the magnetic field. Additional studies, using monoclonal antibodies to detect tumor associated antigens in human colon cancer cells following dose-response and time course exposures to magnetic and electromagnetic fields, indicated that distinct, time dependent changes in specific cell surface antigens of human colon cells could be induced by exposure to magnetic fields (1.0 G RMS) alone and to magnetic fields (1.0 G RMS) in combination with electric fields (300 mA/m^2 current density) (Winters and Phillips 1984b).

In view of observations that magnetic fields may induce cellular mechanisms that are associated or dependent on microtubule organization, Vassilev et al. (1982) studied the influence of magnetic fields on microtubule assembly in vitro using electron microscopic methods. Magnetic fields (0.02 T) applied for 10 min during an in vitro assembly procedure by a constant magnet resulted in parallel arrays of microtubules covering 60% of the total area, while ordered shapes were not found in control unexposed samples.

Recently, Conti et al. (1983) described results of their blastogenesis studies of human peripheral blood lymphocytes stimulated in vitro by nonspecific mitogens (PHA, ConA, PWM) upon exposure to ELF electromagnetic field frequencies of 1, 3, 50, and 200 Hz and field intensities of 23 to 65 G. As measured by ^{3}H-thymidine incorporation, PHA-stimulation was

tumor (SMT-F). Their results indicated that constant magnetic fields of 0.1 to 1.0 T and 60-Hz alternating magnetic fields of 0.1 to 0.16 T for periods of 0.5 to 3 h on consecutive days had no effect on the growth of tumor cells in vitro or in vivo. Using 60-Hz magnetic fields generated by Helmholtz coils of peak intensity of 2.33 mT, Kronenberg and Tenforde (1979) detected no effects of a 1.65-mT, 60-Hz field for up to 100 h on EMT-6 cells.

A pulsed electromagnetic field generated by circular Helmholtz coils was delivered at 6-h intervals for 48 h to cultures of chondroblastic and fibroblastic cells derived from sterna of chick embryos (Norton 1982). Slow growing cultures were stimulated to synthesize hydroxyproline, while rapidly growing cultures showed large increases in lysozyme activity, and in hyaluronate and DNA synthesis. More recently, Colacicco and Pilla (1983) described electromagnetic modulation of ATPase function and DNA production in Raji cells in vitro in their studies seeking mechanisms of coupling of electromagnetic signals with certain cell processes. Their data confirms two important concepts: first, coupling is probably at the plasma membrane level, and second, the effect of the electromagnetic field is conspicuous in the presence of activators or inhibitors, such as ATP in Raji cells and parathyroid hormone in bone cells (Luben et al. 1982).

Using optic microscopic observations confirmed by electron microscopy, Hrehorovsky et al. (1983) detected a several times higher rate of tumor cell (Ehrlich's ascites) nuclei with invaginations compared to control cells following 2-h exposure to magnetic field intensity of 3.6×10^{5} A/m^{-1} over 22 days of study.

In 1983, Liboff and Homer described the relative uptake of ^{3}H-thymidine in human embryonic foreskin fibroblast cultures as a function of low frequency sinusoidal magnetic field intensity. Their results inferred that DNA synthesis in cells exposed to a varying magnetic field was significantly greater than the level in unexposed cells. The effect was observed over a wide frequency range, 10 Hz to 4 kHz, and between 0.2 and 4.0 peak G. Enhancement reached maximum approximately 20 h after the beginning of exposure. Most recently, Liboff et al. (1984) reported that human fibroblasts exhibited enhanced DNA synthesis when exposed to sinusoidally varying magnetic fields over a range of frequencies (15 Hz to 4 kHz) and amplitudes (2.3×10^{-6} to 5.6×10^{-4} T). These experiments showed an interaction, albeit a subtle one, between time-varying magnetic fields (range of 16 to

exposure to electric fields near new power transmission plants and concluded that there was no new evidence to modify the view that electric fields are harmless up to transmission voltages of 400 kV.

IN VITRO STUDIES

Studies began approximately 50 years ago assessing the effects of magnetic fields on the growth of cells in vitro and used permanent magnets producing fields up to 8,000 Oe. Results of such early studies, as summarized by Mulay and Mulay (1964), suggested that retardation of cell growth at 1,000 Oe could occur, while extended exposure for about 3 days at 2,000 Oe could have a growth stimulating effect. Mulay and Mulay (1964), in their studies of Sarcoma ascites mouse tumor (S-37) cells, found that high intensity magnetic fields (4,400 to 8,000 Oe) appeared to cause some degeneration at 37°C after 18 h, while lower intensity fields (100 to 2,000 Oe) had no observed effects after the same period. On the other hand, S-37 solid tumor was not affected by the high magnetic field intensities, which suggests that such fields can have preferential action on certain cells.

Pereira et al. (1967) measured cellular respiration in embryonic mouse kidney and liver, neonatal mouse liver, and adult human cancer ascites sarcoma 37 (S37) and HeLa cells. Applications of fields of 80 to 8F G to S37, HeLa, embryo mouse liver and kidney, and neonatal mouse liver cells produced significant lowering of respiration. Adult mouse kidney and liver cells and older neonatal liver cells were not affected by any fields used. The authors suggested that the more actively proliferating cells were most responsive to fields.

On the other hand, Greene and Halpern (1966) observed no effect on HeLa, WI-38, KB, Chinese hamster, and chick embryo cells in tissue culture after exposure to fields up to 600 Oe under constant environmental conditions for up to 4 days. Likewise, Rockwell (1977) detected no measurable effect on plating efficiency or on growth of EMT-6 mouse mammary tumor cells after 40-h exposure to a 1,400 G magnetic field. Weak magnetic fields were also found to have no significant effect on the growth rate of Chinese hamster V-79 cells grown in a field for more than one year (Sutherland et al. 1978). Chandra and Stefani (1979) studied constant and alternating magnetic fields with respective field strengths of 1.15 T and 0.22 T as they exposed human bronchogenic carcinoma, Raji cells derived from a Burkitt lymphoma, and a transplantable mouse mammary

leukemia for men exposed at work to electrical and magnetic fields. Recently, Milham (1982) suggested an increased risk for leukemia with exposure to electrical and magnetic fields according to occupational designations. A report by Wright, Peters, and Mack (1982), whose findings were consistent with Milham's, suggested that acute myelogenous leukemia is the acute leukemia for which the risk is greatest. While Wright, Peters, and Mack (1982) stated that the precise cause of the excess of the leukemia they observed is not clear and that the occupations grouped as sharing exposures to electric and magnetic fields undoubtedly share other causative exposures, their hypothesis that electric and magnetic fields or other shared exposures cause leukemia deserves further study.

In 1983, McDowall reported on leukemia mortality of electrical workers in England and Wales. His results supported those of Milham (1982), Wright, Peters, and Mack (1982), and Wertheimer and Leeper (1982) in suggesting strongly that persons exposed to electrical and magnetic fields may have an increased risk of leukemia, especially acute myeloid leukemia. No such association was found by Podlenak and Frome (1981) for workers at a uranium-processing plant although the magnetic fields encountered during work were estimated to be of the order of several tens of mT (Easterly 1981).

Data suggesting that exposure to electromagnetic fields may influence reproductive disturbances have recently been reported by Nordstrom, Birke, and Gustavasson (1983). A tendency towards an increased rate of malformations among children whose fathers had worked in 400-kV switchyards was detected. Switchyard workers were found also to have fertility problems more often than workers in other occupations. Since the number of individuals examined in the study was rather small and electric discharges were possible influential factors, the authors indicated that the results, although statistically significant, should be interpreted with caution. More recently, switchyard workers exposed to electric fields were screened for chromosome anomalies in peripheral lymphocytes and rates of chromatid and chromosome breaks were found to be significantly increased as compared to the rates of controls (Nordenson et al. 1984). In this study, the electromagnetic field exposure conditions were not described as the emphasis was on electric field conditions and possible electrical discharge effects.

In contrast to these reports of possible EM effects among electrical workers, Bonnell (1982, 1984) reviewed the literature about the effects of

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EFFECTS OF EXTREMELY LOW FREQUENCY ELECTRIC AND MAGNETIC FIELDS ON THE NERVOUS SYSTEM

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INTRODUCTION

Concern for the possible acute and chronic effects of exposure to extremely low frequency (ELF) (1 to 300 Hz), primarily 60 Hz, electric (E) and magnetic (B) fields has increased over the past decade. The overt cause of this increase has been the widespread construction of high voltage power lines. However, these lines are only the most obvious source of human exposure to E and B fields. Exposure to fields produced by other sources, including a large number of household appliances, is of comparable or nearly comparable intensity and is certainly much more widespread (Bridges and Preache 1981).

The possibility that such almost ubiquitous exposure has deleterious effects has given rise to a broad variety of studies. At one end of the spectrum, epidemiological studies of varying rigor and sophistication have evaluated the health of individuals chronically exposed by occupation or habitation to E and B fields of significant intensity. At the other end are studies exploring field effects in tissue culture and in other reduced preparations. Between these two extremes are a wide variety of more or less controlled laboratory and clinical studies in both animals and humans.

Among the major goals of these studies has been the delineation of field effects on the nervous system. The attention accorded nervous system effects is due to several factors. First, symptoms directly or indirectly referable to the nervous system figured prominently in early epidemiologic studies. Second, and more significantly, the salient features of nervous system function, that is, its reliance on electrochemical phenomena for action potential generation, impulse conduction, and synaptic transmission, strongly suggest that it may be especially susceptible to E and B fields.

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This paper reviews the evidence concerning nervous system effects of ELF E and B fields comparable in intensity to those found in the environment and attempts to evaluate this evidence in terms of the known features of the nervous system and the limitations of our present methods for studying it. While the literature appears at first voluminous, the most cursory examination reveals several features. First, there is an extremely high ratio of secondary to primary papers. The number of articles containing new data is relatively limited. Second, many of those primary sources are quite flawed and unimpressive. This is particularly true for the early epidemiologic studies which reported numerous and prominent but very nonspecific findings suggesting nervous system effects. These reports have not been supported by later, better controlled studies. (The entire body of epidemiologic studies has been reviewed many times and will not be treated here. It is of very little help in assessing nervous system effects.) Major defects are also present in a considerable number of ostensibly well-controlled and rigorous studies. The problems posed by phenomena associated with ELF fields, such as vibration, ozone generation, and microshocks have compromised the data of many studies and greatly complicated interpretation. As a result, the body of reasonably high quality data concerning ELF fields and the nervous system remains limited.

The discussion which follows is divided into seven sections. The first reviews efforts to determine thresholds for field perception in humans and animals. This question is fundamental to the problem of nervous system effects because it addresses the distinction between direct effects on the nervous system and effects on the nervous system due to stress engendered by perception of the fields. The next section, on behavior and performance, concerns observed effects on relatively gross measures of neurologic function. The next discusses effects on circadian rhythms. The next three sections cover more precise techniques for assessing the nervous system: neurophysiologic, neurochemical, and neuropathologic. The final section summarizes our conclusions from the data reviewed in the previous sections.

PERCEPTION OF ELECTRIC (E) AND MAGNETIC (B) FIELDS

A large number of behavioral studies, involving both human and animal subjects, have been carried out to determine whether E and B fields can be detected or perceived. There are a number of important reasons for determining the behavioral thresholds for exposure to these fields. These reasons

include: (1) the necessity, particularly in human studies, for designing experiments employing single or double-blind protocols; (2) the desirability of designing studies capable of separating direct effects of E and B fields from secondary effects due to stress; and (3) the potential insights as to mechanisms of action of E and B fields on the nervous system that might be gained by the study of the small sub-population of humans (<10%) that have been shown to possess increased ability to detect low intensity E and B fields (Graham, Cook, and Cohen 1983).

Human Perception

Comparatively few studies have been conducted on the ability of humans to perceive ELF E or B fields. An even smaller number have been conducted in a scientifically rigorous manner with appropriate nonexposed control groups and with control for extraneous variables that might serve as cues to the presence of the fields. Employing a 10-Hz, 1-G B field, Bil'dyukeyaich, Valeyeva, and Akhmerov (1969) noted a decrease in heart rate during application of the B field. Schmitt and Tucker (1973) and Tucker and Schmitt (1978) exposed humans to 60-Hz, 7.5- and 15-G B fields and noted that the majority of the subjects were able to detect the presence of the B field. However, when the subjects were isolated from the noise and vibration induced by the magnetic coils (the subjects were "housed" in a four-layered plywood box weighing 350 kg suspended from the ceiling by elastic cord and supported by air-filled inner tubes) their ability to detect the presence of B fields was reduced to chance levels. Because such extraordinary efforts were required to isolate the direct magnetic effects from secondary noise and vibration that apparently served as cues for the presence of the B field, one must wonder whether the Bil'dyukeyaich, Valeyeva, and Akhmerov (1969) study and similar studies reporting low B field detection thresholds have adequately isolated the subjects from confounding variables.

Hauf and Weisinger (1973) and Hauf (1976a, 1976b) reported that subjects were unable to detect the presence of a 50-Hz, 15-kV/m E field. These results differ somewhat from the results of a well-designed series of experiments recently conducted by Graham, Cook, and Cohen (1983). These authors controlled for factors thought to influence human perception of E and B fields, including ambient temperature, humidity, type of clothing worn, contact to ground, and time of day when testing took place. Subjects were exposed to

60-Hz, 0- to 15-kV/M E fields and 0- to 0.4-G B fields. Graham and coauthors (1983) employed a psychophysical method of limits. Subjects were unable to perceive B fields of any intensities. E field detection occurred at a mean intensity of 14.6 kV/m (9/24 subjects reported no E field perception). Subjects who reported perception of the field described the exposure as a "tingling" feeling. In addition, the study noted no difference in E field thresholds as a function of time of day, but found that when the subjects stood with their arms raised, the detection threshold was lowered to approximately 8.0 kV/m. Thresholds for perception increased as a function of exposure duration and number of exposures to the E field.

These laboratory studies are partially supported by field studies that have employed transmission lines as sources of the E and B fields. Both Zafanella (1972) and Delaplace and Reilly (1978) reported human perception of E fields in the range of 10 to 20 kV/m. A small sub-population (10% of Delaplace and Reilly's 110 subjects) reported that the presence of the fields was annoying.

Animal Perception

Considerably more studies have been conducted on the ability of animals to detect the presence of E and B fields. These studies may be divided into three categories: (1) those employing high intensity E fields (30 to 120 kV/m) in which the preference of animals for shielded versus unshielded sides of runways or mazes is determined; (2) those using lower intensity field exposures (<20 kV/m) in which animals are trained on operant-psychophysical detection tasks; and (3) those primarily involving migratory or homing behavior in birds exposed to weak E and B fields.

Hjeresen et al. (1980) exposed rats to 60-Hz, 25- to 105-kV/m E fields and allowed the animals to chose between shielded and unshielded sides of a shuttlebox. The animals showed a clear preference for the shielded side at E field intensities of 75 kV/m or greater and no preference at 25- or 50-kV/m intensity. In a similar study, Hjeresen et al. (1982) exposed swine to a 60-Hz, 30-kV/m E field for 20 h/day for six months and determined their preference for the shielded versus the unshielded side of a shuttlebox. The swine spent more time in the shielded side of the box, although their preference was most marked during the dark portion of the light-dark cycle. Mechanisms of perception of these high intensity E fields may involve hair or

vibrissae movement since Phillips and Kaune (1977) noted hair stimulation (piloerection and hair oscillation) at E field intensities of 50 kV/m.

Both Creim et al. (1983, 1984) and Lovely (1982) exposed rats to 60-Hz E fields at intensities up to 100 kV/m and determined both preference for the shielded versus the unshielded side of a shuttlebox and the amount of saccharin-flavored food (located on the exposed side) consumed by the rats. In both studies, rats avoided E fields over 75 kV/m and consumed significantly less saccharin-flavored food. However, Lovely (1984) has subsequently demonstrated that the location of the food cup plays an important role in influencing the aversive behavior: if the food cup is located above the ground plate the animal will develop an aversion to the saccharin-flavored food; if the food cup is located below the ground plate the animal will continue to consume the food, even in the presence of the E field. Apparently the causative factor in inducing the aversive behavior were microshocks the animal received when feeding. In both an interim report (Lovely 1982) and a later publication (Creim et al. 1984), pairing of 60-Hz, 34-to 133-kV/m E fields with saccharin-flavored water consumed before entry into the E field failed to produce a conditioned taste aversion to the flavored water. Failure to induce taste aversion may be due to the fact that, in the latter studies, animals were exposed for only 3 h and preference was determined in the absence of the E field. These findings are also consistent with the possibility that, although the animals can detect the field, they do not find it aversive. A preference for one of two stimuli (field on or field off) does not necessarily imply that the nonpreferred stimuli is aversive: the E field may be avoided by the animals simply because it is novel and unfamiliar. Although animals may demonstrate a rapid adaptation to the presence of a continuous field, a shielded/unshielded two-choice experimental paradigm allows the animal to make multiple, short-term entries into the E field, hence adaption to the novel aspects of the E field may not occur. However, continued preference over repeated trials would suggest that the field may indeed be aversive.

Clarke and Justesen (1979) tested chickens for perception of either a 40-G DC B field or a 17-G AC field, by pairing the presence of the B field (the conditioned stimulus) with electric shock (the unconditioned stimulus) during operant responding for grain. The presence of the conditioned stimulus significantly increased the variability of responding, suggesting that the birds could perceive the AC B field. Using a similar paradigm (conditioned

suppression of operant responding) Graves (1981) exposed pigeons to a 60-Hz, 50-kV/m E field in either shielded or unshielded test cages. Because both test units were exposed to the same noise and vibration from the electrical generating equipment, secondary perceptual cues were ruled out. Pigeons exposed to the E field demonstrated significant suppression of operant responding, whereas Faraday-shielded pigeons did not, indicating perception of the E field. In a well-designed experiment, Stern et al. (1983) employed a psychophysical sensory detection technique (rats were trained to barpress for food only during the presence of a 60-Hz E field) and varied field intensity between 0 and 10 kV/m. Detection thresholds were found to be between 4 and 8 kV/m.

The effects of weak static magnetic fields (0.6 G) on homing behavior of pigeons were investigated by Walcott and Green (1974) who attached small magnetic coils to the heads of the pigeons. When the south magnetic pole was oriented up there was no effect; however, when the polarity was reversed homing behavior was adversely affected, but only under cloudy conditions. Similar results were found by Wiltschko and Wiltschko (1972) who noted that pigeons deprived of the use of their sun-compass by dark-rearing were disoriented when carrying magnets. Papi, Meschini, and Baldaccini (1983) exposed homing pigeons to sinusoidal AC B fields with periods of either 15, 23, or 29 s at intensities of up to 0.6 G, either at their home nest or during transportation to the release site, and noted decrements in the birds' initial orientation behavior, with exposure during transport being most effective. Larkin and Sutherland (1977) radar tracked migratory birds flying over a 24-km long antenna similar to that designed for the Navy Seafarer Project (at 40-m, E fields were approximately 0.07-V/m and B fields were .001 to .005 G at 72 to 80 Hz). When the antenna was activated, birds turned or changed altitude more frequently than when the antenna was inactive. This exquisite sensitivity to extremely weak B fields has been hypothesized to be due to the presence of a specialized magnetoreceptor structure located between the skull and brain (Walcott, Gould, and Kirschvink 1979) or in neck musculature (Presti and Pettigrew 1982).

In summary, except for avians which may possess specialized receptors thought to be used for homing and migratory behaviors, the ability of animals to detect B fields in the range of 60 Hz, in the absence of secondary cues such as noise and vibration, is minimal. On the other hand, available data

ıggest that both humans and laboratory animals can detect 60-Hz E fields at ıtensities between 4 and 15 kV/m. A subset of the exposed human population ıpproximately 10%) describe the higher intensities as annoying. Cues, other ıan noise and vibration caused by the generating equipment, may include pilo-ection or hair movement and a "tingling" sensation in glabrous portions of ıposed skin. Preference for the shielded side of a shuttlebox at intensities greater than 30 kV/m would suggest that the E fields may be aversive, lthough Creim et al. (1984) were unable to produce a conditioned taste version to saccharin in rats exposed to E fields of up to 130 kV/m, suggest-ıg that the positive incentive value of the saccharin-flavored food or water vercame the weak aversive nature of the E field.

FFECTS ON BEHAVIOR AND PERFORMANCE

Exposure to ELF B fields have been associated with changes in behavior. dult rats exposed to a 0.5-Hz, 3-to 30-G B field (produced by rotating a orseshoe magnet) for 21 to 30 days were shown by Persinger, Ossenkopp and alvin (1972) to be more active in an open field following the exposure eriod, relative to nonexposed controls. Ossenkopp and Ossenkopp (1983) found hat exposure to a 0.5-Hz, 3-to 30-G rotating B field for up to 30 days esulted in increased open-field activity in male, but not female, rats. The fields used in the studies by Persinger, Ossenkopp, and Galvin (1972) and ssenkopp and Ossenkopp (1983) were generated by rotating a horseshoe magnet irectly under the animals' cages using electric torque motors. Control nimals were housed 1 to 2 m away from the exposed animals, where the B field as shown to be negligible. Control animals did not have an electric motor nder their cages. The cages of the exposed animals were placed on a 5-cm hick foam pad to provide insulation from possible vibrations induced by the lectric motor. Unfortunately, it was not demonstrated that the foam ade-uately dampered vibration produced by the motor. Given the exquisite vibra-ion sensitivity of humans (Tucker and Schmitt 1978), more rigorous controls ill be necessary to prove that vibration was not causing the B field effects bserved in these studies. Furthermore, it is not clear from these studies hether the observed effects on behavior were due to the rotating B field or exposure to the electromagnetic field generated by the electric motor otating the magnet.

Persinger (1969), using apparatus identical to that used by Persinger, enkopp, and Galvin (1972) and Ossenkopp and Ossenkopp (1983), reported that e, but not female, rats prenatally exposed to a 0.5-Hz, 3-to 30-G B field wed a decrease in open-field activity levels that did not differ from trol animals (housed 1 to 2 m away from the electric motors). This evi- ce suggests that the decrease in activity associated with B field exposure not due to vibration or E fields produced by the electric motor. It is clear whether the different effects of B field exposure on activity cribed by Persinger (1969), where activity decreased following exposure, that described by Persinger, Ossenkopp, and Galvin (1972) and Ossenkopp Ossenkopp (1983), where activity increased following exposure, was due to sible vibration or E field effects produced by the electric motors, or resented differences related to prenatal versus postnatal exposure.

ELF B fields have also been reported to affect human behavior. Friedman, ker, and Bachman (1967) reported that a 0.2-Hz, 5- to 11-G B field increased ction time by approximately 40 ms (15[illegible]) in humans. A 0.1-Hz, 5- to 11-G B ld was without effect. It was not clear from this study why a 0.2-Hz B ld would have an effect but a 0.1-Hz field would not. This effect was, ever, seen by Friedman, Becker, and Bachman (1967) in two separate eriments.

Studies using ELF B fields with frequencies greater than or equal to 7 Hz e in general reported no effects on behavior. Gibson and Moroney (1974) ld find no effects on measures of memory, response times, or tracking lity during 24-h exposure to a 45-Hz, 1-G B field. de Lorge (1974) exposed keys to 45- and 15-Hz, 1-G B fields during behavioral testing. No effect observed on an inter-response time (IRT) task, where monkeys had to pond 5 to 6 s following a stimulus to receive reward (responses occurring ore 5 s or after 6 s were not rewarded). Grissett and de Lorge (1971) osed monkeys to 7- and 45-Hz, 3-G B fields during behavioral testing. No ects were found on reaction time. Grissett (1971) has also looked at the ect of long-duration B field exposure. Monkeys were exposed to a 45-Hz, G B field for 23 days. No effects on reaction time could be detected. de ge and Grissett (1977) looked at the effect of 7-, 10-, 45-, 60-, and Hz, 3- to 10-G B fields for up to 42 days. No effect could be detected on ction time, on IRT, or on performance on a memory test.

There have also been reports that ELF E fields can affect behavior.

las-Medici and Day-Magdaleno (1976) reported that exposure to 7- or 75-Hz elds at intensities of only 1 to 56 V/m produced a change in IRT respond- in monkeys. Monkeys were found to respond about 5% faster when the E d was on than when the E field was off. At the 7-Hz exposure, the thres- for change in IRT responding was 10 V/m. Effects at 75 Hz were only seen he highest intensity used (56 V/m). No change, however, was seen on IRT onse during exposure to a 60-Hz, 56-V/m E field. Preliminary work by rs (1982) has shown that baboons exposed to a 30-kV/m, 60-Hz E field for lays exhibited an increase in startle responses and a general decrease in vity (i.e., less exploring and locomotion behaviors). Lovely, Creim, and lips (1983) did not report any change in activity in the second generation geny of miniature swine exposed to 60-Hz, 30-kV/m E fields. They did note, ever, that female swine subjects vocalized less than exposed controls. . (1964) noted increased activity in mice exposed to 60-Hz, 80-120 kV/m E lds. Similarly, Duffy and Ehret (1982) exposed mice to 60-Hz, 10-75 kV/m E lds for 4 one-hour sessions and demonstrated increased locomotor activity n intensities over 50 kV/m.

ELF E field exposure has been reported to affect performance in humans. ig (1974) reported that 3- to 10-Hz, 2- and 7-V/m E fields changed reaction es in humans. Exposure to a 3-Hz, 4-V/m field was reported to increase ction time whereas exposure to a 6- or 12-Hz, 4-V/m E field was said to rease reaction time. These changes were small (< 5%) and statistical lysis was not performed on the data, hence it is not clear if they were nificant. Persinger, Lafreniere, and Mainpute (1975) were unable to find effect of a 3- or 10-Hz, 3-V/m E field on reaction time to humans. They , however, report a small decrease in reaction time variability during osure, but were doubtful as to its significance.

The evidence described above suggests that ELF E and B fields can affect ivity levels of rodents and monkeys. Low frequency rotating B fields and Hz alternating B fields were shown to increase activity of rats and mice. fact that B fields alternating at greater than 7 Hz generally had no ect on activity suggests that the B field-induced change in activity might frequency specific. Unfortunately, studies using B fields that alternated greater than [illegible] used lower intensities than studies of B fields alternat- [illegible] Thus the lack of effect may be due to differences in [illegible] rather than the frequency of the B field. E fields of 60 Hz

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10 kV/m). E fields of such intensity probably have modest effects on mammalian nervous systems. Mechanisms remain unclear. Direct nervous system effects of field exposure appear to occur only at much higher exposure levels. This implies that effects seen at environmental levels may be mediated via some receptor or transducer mechanism or through effects on another body system. Most important, any effects at environmental exposure levels appear to be no more severe than effects which may be produced by exercise, work schedule changes, exposure to novel stimuli, or minor stress of other origins. There is no convincing evidence that ELF E or B fields of environmental intensity harm the nervous system, exceed its adaptive capacities, or produce significant functional changes. The available evidence suggests that any effects which do exist are modest and well within physiologic limits.

The literature suggests that organisms may be particularly sensitive to perturbation by E or B fields of less than 10 Hz (Dowse 1982; Dowse 1969, Gavalas et al. 1970; Wever 1967, 1970). Explanations for these apparent frequency-window effects are based either on the fact that mammalian EEG frequencies are in the same range or the fact that the earth's naturally occurring fields are less than 10 Hz. In order to confirm these hypotheses based on experiments conducted in different laboratories with different species, measuring different physiological endpoints at different field voltages, it is necessary to generate frequency and dose response curves for a wide range of the relevant, objective physiological endpoints.

Thus, the available literature strongly indicates that future work should proceed in more organized and logical fashion. To the greatest extent possible, there should be standardization of species, frequencies, intensities, exposure schedules, and exposure durations. All recognized complicating factors need to be rigorously controlled. At least initially, E and B fields should be studied separately. These recommendations appear essential if E and B field effects on the nervous system are to be significantly elucidated in the near future.

may be due to the stress of exposure to a novel or mildly aversive stimulus (E or B fields) rather than to direct E field effects.

NEUROPATHOLOGIC EFFECTS

Relatively few pathologic studies have been performed in exposed animals and the data which are available are not in agreement. Dumansky, Popovich, and Prokhvatilo (1976) reported significant pathologic findings in rats exposed to 2- to 5-kV/m fields for 4 months. In more complete studies the Battelle group (1978) found no evidence of CNS pathology in mice exposed to a 60-Hz, 65-kV/m E field for 1 month. Hansson (1981a, 1981b, 1984) has reported severe changes in cerebellar Purkinje cells and glia in rabbits perinatally exposed for 1 to 2 months to 50-Hz, 14-kV/m fields. However, growth was markedly impaired in exposed animals, so that the specificity of the observed neuropathologic effects remains unclear.

Very limited data are available in regard to ELF B fields. Toroptsev and Soldatova (1981) reported edematous changes in the cortex of rats exposed to a 50-Hz, 200-G field for 6-1/2 h. In contrast, Friedman and Carey (1969) noted no changes in the brains of rabbits exposed for 60 h, to .1- to .2-Hz fields of up to 170 G.

At present, it is not possible to reach any even tentative conclusions as to the neuropathologic findings in ELF-exposed animals.

SUMMARY AND CONCLUSIONS

A considerable number of studies have investigated ELF E and B field effects on the nervous system. For the most part, results are inconsistent and confusing and hence difficult to interpret. Many factors have undoubtedly contributed to this unsatisfactory situation. Studies have varied widely in animal species, field frequencies and intensities, exposure schedules and duration, and parameters measured. Complicating factors, such as corona and microshocks, have often gone unrecognized or have been inadequately controlled. There may well be other as yet unrecognized complicating factors which may, for example, account for the frequent disconcerting variability of results generated within a single laboratory. One such factor may be seasonal fluctuations in sensitivity to field effects.

In spite of the present uncertainties, we can reach a few tentative conclusions concerning E fields of environmental intensity (i.e., about

E and B fields varies with the endogenous circadian rhythm of the animal and that the experimenter should consider this when planning experiments involving brief (<24 h) exposure to E and B fields.

Michaelson, Altman, and Quinlan (1981) exposed Long-Evans rats to 60-Hz, 100-kV/m E fields for 1 to 3 h and determined whole brain catecholamine concentrations. Dopamine, L-DOPA, and norepinephrine concentrations were elevated compared to sham-exposed rats. Dixey and Rein (1982) exposed a pheochromocytoma cell line (PC12) to a 8.5-G B field pulsed at 500 Hz (.6 ms-on, 1.4 ms-off) and noted a 28% increase in the release of ^{3}H norepinephrine at 105 and 120 min after exposure to the B field. No increases in the temperature of the medium were noted. Employing a novel exposu paradigm, Kaczmarek and Adey (1974) exposed gallamine-immobilized cats to weak E fields via agar electrodes placed directly on the cortex. This procedure produced fields from 24 to 60 mV/cm depending on the depth measured below the cortex. The cortex was bathed in a physiological medium containing $^{45}CaCl_2$ and [^{3}H] GABA for 3 h prior to E field exposure which consisted of a stimulus train of 1-ms pulses at 200 Hz. Exposure resulted in stimulus-bound increases in release of ^{45}Ca and [^{3}H] GABA.

Except for the Dixey and Rein (1982) study which employed sharp, non-sinusoidal pulses and the somewhat unorthodox exposure paradigm employed by Kaczmarek and Adey (1974), no studies have determined the effects of E field exposure on turnover of neurotransmitters. Measurement of steady-state concentrations of neurotransmitters provide no information on the activity of neurons. Studies employing synthesis inhibitors such as alpha-methyl para-tyrosine, concomitant measurement of neurotransmitters and their metabolites, or measurement of L-DOPA concentrations following dopa-decarboxylase inhibition are necessary to determine whether E or B fields affect neurotransmitter turnover. Furthermore, as alluded to in the beginning of this section, techniques have been developed and refined to estimate central neuronal (primarily catecholaminergic) activity in man by determining circulating concentrations of catecholaminergic metabolites or by measuring their concentrations in 24-h urine collections. It is hoped that these techniques will be applied to investigate neurochemical function in man following exposure to E and B fields.

In conclusion, E field exposure can effect chemical transmission in nervous tissue, although neurotransmitter changes seen during brief exposures

the effects of low level B and E fields on the nervous system are probably mediated by a receptor mechanism. Although an E or B field receptor has not yet been conclusively demonstrated, several types have been proposed, including magnetic material present in the skull and muscle, and $^{2+}$Ca binding to glycoproteins in the neuronal cell membrane.

NEUROCHEMICAL EFFECTS

In spite of the obviously important role that neurotransmitters play in regulating the behavior of the organism and the physiology of the nervous system, surprisingly few studies have been conducted on the effects of E and/or B fields on neurochemical measures. Indeed, the only attempt to measure metabolites of catecholamines (e.g., homovanillic acid, DOPAC, MHPG) in urine or plasma of humans exposed to E or B fields is the study conducted by Graham et al., the results of which are not yet available. Thus, this review of the neurochemical data is, of necessity, restricted to animals.

Krueger, Yost, and Reed (1980) exposed successive generations of mice to 76-Hz E and B fields of intensities similar to that produced by the Navy's project Sanguine-Seafarer and measured serotonin (5-HT) concentrations in blood. No changes in circulating concentrations of 5-HT were noted. Wilson et al. (1981) exposed rats to 60-Hz electric fields of 65 kV/m intensity 20 h/day for 30 days and determined that the normal nocturnal elevation in pineal melatonin concentrations was significantly depressed in exposed animals. The nocturnal activity of serotonin N-acetyl transferase (an enzyme that converts 5-HT to the melatonin precursor N-acetyl serotonin) was reduced and concentrations of 5-methoxytryptophol were increased, suggesting that the preferred synthetic pathway (5-HT → N-acetyl-5HT → melatonin) may be partially shunted to the less preferred (5-HT → 5-OH tryptophol → 5-methoxytryptophol) pathway by E field exposure. Although these results have subsequently been replicated, equipment failure during the original experiment reduced E fields to 1.7 to 1.9 kV/m, suggesting either that the observed effects were due to factors other than the E field or that pineal melatonin synthesis is extremely sensitive to E fields. If the alterations in pineal melatonin synthesis are due to exposure to E and/or B fields, they may provide a biochemical basis for the proposed behavioral alterations in circadian activity induced by the E and B fields. Indeed, these studies would suggest that the biochemical (and perhaps) the behavioral sensitivity of the animal to

canals of the vestibular system as an excellent candidate for such a system since it approximates a one-turn coil, is filled with a highly conductive fluid, and is heavily innervated. However, based on their calculations, they determined that currents generated by B fields of approximately the same amplitude as the earth's B field would be of the same order of magnitude as that generated by thermal noise. Thus, it seems unlikely that this kind of mechanism could be used to transduce B fields of less than 1 G. The failure of Tucker and Schmitt (1978) to find evidence of human perception of 60-Hz B fields of up to 15 G suggests that B field transducing systems do not provide supraliminal output at such higher B field intensities either, at least in humans.

Exposure to very weak ELF E fields and ELF amplitude-modulated microwave E fields has been shown to alter $^{2+}$Ca efflux from cat and chick brains (see Adey 1981 for review). Adey and his coworkers found that 16-Hz E fields decreased $^{2+}$Ca efflux from chick brain by 12 to 15% (Bawin, Sheppard, and Adey 1978). The reason for this discrepancy is not clear but may be related to differences in the exposure facilities (Blackman et al. 1982). Microwave E fields amplitude-modulated at 16 Hz have been reported to increase $^{2+}$Ca efflux from chick and cat brains (see Adey 1981 for review). While some question the direct effect of E fields on $^{2+}$Ca efflux (Myers and Ross 1981), this phenomenon might provide a mechanism for transducing weak ELF E fields. Adey (1981) has suggested that the effect of ELF radiation on $^{2+}$Ca efflux is due to alteration of $^{2+}$Ca binding to glycoproteins located on the cell membrane. He has hypothesized that the altered $^{2+}$Ca binding might produce conformational changes in these proteins that could change cell excitability. Changes of this kind could conceivably account for the slight field effects on synaptic transmission reported by Jaffe (Jaffe, Laszewski, and Carr 1981; Jaffe et al. 1980).

At present, the combined impact of these studies is that E fields at or somewhat above powerline intensity may have modest detectable direct effects on neuronal activity. However, there is at present no neurophysiologic data indicating that those effects are nonphysiologic, that they exceed the normal adaptive capabilities of the nervous system, or that they have any deleterious effects on the function of the intact organism. Furthermore, the evidence described in these studies implies that it is very unlikely that low level B and E fields exert a direct effect on the excitability of nerve cells. Thus,

and Kirschvink (1979) have suggested that the magnetic particles align themselves with the earth's B field and in so doing create a torque which somehow activates nerve fibers thought to innervate these particles. There have been recent demonstrations of magnetic material in the skulls of certain mammalian species, including dolphins, woodmice and humans (Gould 1984). This magnetic material may be involved in transducing B fields in mammals, including humans, as well as in birds.

Delgado and Bustamante (1984) reported in a preliminary study that crab stretch receptors were affected by 0.3-Hz B fields of less than 1 G. Whether magnetic particles such as those in birds are present and responsible for the observed effects remains to be determined.

Lovsund, Oberg, and Nillsson (1979) have determined the threshold for induction of magnetophosphenes in humans. Magnetophosphenes are tiny spots of light perceived by a subject exposed to a B field. Lovsund, Oberg, and Nillsson (1979) reported that sensitivity was maximum at 20 Hz, where threshold was about 10 G. Lovsund, Nillsson, and Oberg (1981), studying the effects of B fields on the activity of neurons in the frog retina, suggested that induction of magnetophosphenes was due to excitation of sensory receptors in the retina by the B field and was not due to direct activation of retinal neurons.

Weigel and Jaffe (1983) investigated the sensitivity of cat cutaneous receptors to 60-Hz E fields and found that the most sensitive responded to fields of 160 kV/m or greater. Given that the currents induced by this field are insufficient to directly initiate nerve cell discharge (see above), it is possible that the E field was directly activating cutaneous receptors. It should be noted, however, that the currents induced by this E field are within the magnitude that has been shown to affect neuronal excitability, and hence might simply have lowered the afferent fibers threshold to natural cutaneous input. Nevertheless, direct activation of cutaneous receptors is unlikely to be the mechanism responsible for perception of E fields (discussed in an earlier section) since the E field intensity required to initiate firing in cutaneous afferent fibers (160 kV/m) is much greater than that required for perception (<20 kV/m).

Jungerman and Rosenblum (1980) considered the possibility that weak B fields might be detected by currents generated in conductive tissue as an animal moves through a B field gradient. They considered the semicircular

where J is the current density, E is the electric field gradient, and σ is the conductivity of the tissue (1/resistivity) (Nunez 1981). A 35-mV/cm E field is just sufficient to affect neuronal excitability (Abu-Assal et al. 1984). The current induced by this field is:

$$J = (300 \text{ ohm/cm})^{-1} \times (35 \times 10^{-3} \text{ V/cm}) = 116.7\ \mu A/cm^2.$$

Thus, it appears that an extracellular current on the order of 100 $\mu A/cm^2$ is needed to change neuronal excitability in mammalian nervous tissue. Generating current densities of this magnitude in the nervous system would require an extraordinarily large E field in air. Deno (1979) and Lovstrand et al. (1979) have estimated that a human standing in a 10-kV/m E field, such as would be experienced under a 750-kV powerline, would experience a current density of less than 1 $\mu A/cm^2$ through the head and neck region. Maximum current in this situation is found in the lower leg region (e.g., ankles), however, even here current is only approximately 3 $\mu A/cm^2$ (Bridges and Preache 1981). Thus, currents generated in the body by an E field such as that experienced under a 750-kV powerline are approximately two orders of magnitude smaller than that required to alter neuronal excitability in mammals. It seems unlikely that such currents would have detrimental effects on the nervous system since these currents are much less than those generated by synchronously firing neurons (Jefferys 1983; Taylor and Dudek 1984). Thus, direct modification of neuronal excitability might only be expected under conditions of very high E fields in air, and hence is unlikely to be mediating the neurologic effects of weak E fields.

ELF electromagnetic fields might also affect the nervous system through action on a sensory receptor. Sensitivity to weak ELF fields and the mechanisms by which these fields are transduced have been studied most extensively in fish and birds (Gould 1984). Many species of fish are known to use ampullary receptors, located on their skin surface, to sense very small E field gradients on the order of 1 mV/cm (Bullock 1977). An electric field gradient results in transmitter release from the sensory cells which causes a train of nerve impulses in fibers innervating these cells (Bullock 1977).

The sensitivity of certain bird species to very weak B fields may be due to magnetic material within the skull (Walcott, Gould, and Kirschvink 1979) and/or in the neck musculature (Presti and Pettigrew 1982). Walcott, Gould,

section EFFECTS ON BEHAVIOR AND PERFORMANCE). The change in muscle fatigue recovery might, for example, be a normal physiologic response to chronically increased or altered gross motor activity due to field exposure.

In addition to the studies discussed so far which have attempted to detect effects of whole-organism exposure, there have been other studies, using reduced preparations, directed at determining the sensitivity of nervous system function, specifically neural firing, to field exposure. These studies address the question of whether fields of powerline frequency and intensity could conceivably directly affect neuronal activity.

Extremely high E field intensities (10^6 V/m) in air would be required to produce body currents of sufficient intensity to directly initiate nerve cell discharge (approximately 1 to 2 mA/cm^2) (Bernhardt 1979). Thus, E fields typically encountered in the environment would not be expected to directly initiate nerve cell discharge. However, electric fields of much lower intensity might affect the excitability of neurons. Wachtel (1979) demonstrated that firing of <u>Aplysia</u> pacemaker cells is affected by 1- to 60-Hz electric currents of 1 to 40 $\mu A/cm^2$, comparable in intensity to those produced in humans by powerline exposure.

Much higher currents, however, seem to be required to affect the firing of mammalian neurons. Jefferys (1983) has shown that weak E fields (presented as pulses lasting 25 to 250 ms) of the order of 5 mV/mm changed the excitability of granule cells in the hippocampal dentate gyrus to afferent stimulation. Abu-Assal et al. (1984) have also shown that weak 60-Hz E fields of the order of 3.5 to 5.0 mV/mm can affect the excitability of hippocampal neurons. These changes in neuronal excitability were highly dependent upon the orientation of the applied field with respect to the cells.

The change in neuronal excitability due to extracellular voltage gradients observed in these studies has been attributed to leakage into the cell of a small fraction of the extracellular currents produced by the E field (Jefferys 1983; Taylor and Dudek 1984). Assuming a tissue resistivity of 300 ohm/cm (Nunez 1981), one can estimate (within an order of magnitude) the current density produced in the Jefferys (1983) and Abu-Assal et al. (1984) studies from the relationship:

$$J \quad \cdot E,$$

nemestrina) via implanted electrodes. The principal finding was revealed by frequency analysis and consisted of increased activity at the frequency of the applied field. The significance of these data remains unclear. It seems possible that the finding is an artifact, due to direct pickup of the imposed fields by the recording electrodes. The extreme sensitivity of EEG to such artifacts and the apparent absence of other more definite physiologic changes in the data are consistent with this possibility. EEG recording in the period following exposure might have helped resolve this question. In light of this uncertainty, and the numerous studies failing to detect effects of much stronger (albeit higher frequency) fields, this study requires confirmation and expansion. At present, available studies fail to provide any strong evidence that fields of powerline frequency and intensity affect the EEG.

Other than the EEG studies summarized above, there have been few studies which have used neurophysiologic methods to search for ELF effects in the whole animal. In an impressive series of studies over the past decade, Jaffe and colleagues (Jaffe, Laszewski, and Carr 1981; Jaffe et al. 1980) have studied synaptic transmission, nerve conduction, and neuromuscular function in rats exposed to a 60-Hz, 65-kV/m E field for 30 days. At the end of exposure, animals were sacrificed and comprehensive in vitro studies were conducted. Of the multiple parameters measured, only two were consistently affected by exposure. First, in tests of synaptic transmission in the superior cervical ganglia, the conditioning-test response, (a measure of the effect of a single stimulus on synaptic function) was altered. Specifically, the response to a second stimulus was moderately larger in exposed than in control animals. While this finding appears real, its meaning remains unclear, especially in the absence of alterations in other related measures of synaptic function. Second, in extensive tests of neuromuscular function, only fatigue recovery of slow twitch muscle was affected. It was modestly enhanced by field exposure. Again, the meaning is unclear. The authors speculate that it may be secondary to vascular or metabolic effects. These studies indicate that while prolonged, relatively intensive E field exposure has isolated, modest detectable effects on synaptic transmission and neuromuscular function, these effects appear minor and certainly do not move nervous system function out of the normal physiologic range. Their origin is unclear. They could be due to direct field effects on neurons, to effects on other body systems, or perhaps to the changes in overall activity which may be produced by exposure (see

other laboratories weakens the ability of reviewers to conclude definitely that naturally occurring E fields entrain the activity of humans. However, Dowse (1982) has demonstrated that exposure to 10-Hz weak E fields can alter the circadian activity of free-running Drosophila melanogaster. The fact that Ehret and colleagues (Duffy and Ehret 1982; Ehret 1982; and Ehret et al. 1981a, 1981b) needed to expose mice to very strong electric fields (130 kV/m) to induce phase shifting may have been due to the fact that they used 60-Hz E fields.

NEUROPHYSIOLOGIC EFFECTS

The electroencephalogram (EEG), the voltage changes produced at the scalp by activity in the underlying brain, is composed of ongoing, spontaneous activity and activity linked to particular stimuli (i.e., evoked potentials). It provides noninvasive means of studying the central nervous system (CNS). While the EEG is a very complicated product of activity in many regions of the CNS, and is therefore removed from the basic processes underlying it, it has proved a sensitive measure of CNS function in many situations. Alterations in EEG frequencies and amplitudes, either generalized or confined to specific scalp regions, have proved invaluable in detection and evaluation of a wide variety of CNS abnormalities, both diffuse and focal. Evoked potentials furnish quantitative assessment of function of the CNS sensory systems: visual, auditory, and somatosensory.

A number of studies have examined the EEG in humans or animals exposed acutely or chronically to E and/or B fields of intensities comparable to those encountered under high-voltage powerlines. With few exceptions the results have been negative. In acute studies in humans, Hauf (1974, 1976a) and Schuy and Waibel (1979) failed to detect any EEG changes with exposure to 50-Hz, 20-kV/m E fields. In a preliminary report, Silny (1976) noted no significant EEG changes in cats and rats exposed for 6 to 8 h to power frequency fields of 60 and 80 kV/m respectively. In chicks exposed over 3 weeks to 60-Hz fields of up to 80 kV/m, Graves et al. (1978) noted no changes in EEG recorded via electrodes implanted after field exposure. Jaffe et al. (1983) studied the visual evoked potential in rats exposed for postnatal days 11 to 20 to a 60-Hz, 65-kV/m E field. No effects were noted.

In contrast to these negative studies, Gavalas et al. (1970) reported that 7- and 10-Hz fields of only 7 V/m affected EEGs recorded from monkeys (Macaca

1975), exposed subjects demonstrated a circadian periodicity of 24 h, providing further support for the concept that electric fields may act as an entraining stimulus or zeitgeber.

In contrast to the lack of effect of artificial DC fields on human circadian activity, Dowse and Palmer (1969) exposed mice in wire cages with attached running wheels to an electrostatic field produced by charging the cages to 500-V DC and noted an approximately one hour decrease in the circadian period. It should be noted, however, that the authors stated that the complicated shape of the cage and local intensity differences of this very nonhomogenous field were virtually unmeasurable, making comparison to other studies difficult. Duffy and Ehret (1982), Ehret (1982), and Ehret et al. (1981a, 1981b) exposed mice living under constant dark conditions to two 0.5-h vertical E field exposures of 60 Hz at an intensity of 100 kV/m. Exposure during the early, active phase of the circadian rhythm resulted in a significant (3.3 h) phase delay compared with controls, while exposure during the inactive phase resulted in an approximate 4.1-h advance. Accompanying these phase shifts were alterations in activity observed during time of field onset and offset and increased CO_2 production. When field exposure was increased to 9 h, circadian phase delays were increased to approximately 6 h and were accompanied by prolonged periods of inactivity or torpor. Whether these phase shifts represent true changes in an internal biological clock or are secondary to changes in activity induced by the exposure paradigm remains unclear. However, these results must be considered tentative at best because Ehret has induced phase shifts in only one species of mice, Peromyscus leucopus, and with only one electric field (130 kV/m). Until this work is repeated with other mouse strains, and indeed with other species, the effects of E fields on circadian activity in rodents must be considered a tenuous finding.

Employing a 12-h on, 12-h off, 10-Hz, 150-V/m E field, Dowse (1982) determined phase shifts in the locomotor activity of Drosophila melanogaster maintained under constant illumination. Exposure to this weak E field induced a phase shift advance of 6 h.

In summary, free-running rhythmic (circadian) activity can be affected by exposure to E and B fields, although the mechanisms by which such changes occur have not been elucidated. The strongest evidence for such effects are the long series of human studies reported by Wever (1967, 1970, 1973, 1974a, 1974b, 1977). The fact that similar studies have not yet been carried out in

were reported to decrease activity in baboons but not in rodents. This latter finding will have to be replicated before conclusions about species differences in the effects of E fields on activity can be made. The evidence described above also suggests that E and B field exposure might have effects on other behaviors. However, the different field frequencies, levels, exposure durations, and times of testing with respect to exposure, and the different dependent variables measured by the different investigators make these possible effects difficult to evaluate. Clearly, more work is required to replicate these results and to determine the dose and frequency responses of the effects with standard behavioral tests before the results can be interpreted in a meaningful manner.

EFFECTS ON CIRCADIAN RHYTHMS

All living organisms display rhythmic changes in physiology and behavior in the absence of perceptible external timing cues. Because these rhythms generally approximate 24 h in length, they have been termed circadian (circa = approximately; dies = day) and are thought to represent external manifestations of internal biological clocks. Interest in the possible effects of weak E and B fields on circadian activity stems from the fact that the natural geoelectrostatic field (>130 V/m) undergoes a daily 15 variation in intensity and may therefore act as an entraining stimulus for circadian activity.

In a series of studies beginning in 1967, Wever (1967, 1970, 1973, 1974a, 1974b, 1975, 1977) investigated the effects of naturally occurring E and B fields in artificially-induced E fields on circadian activity humans. Subjects were housed for periods of 3 to 8 weeks in underground bunkers where locomotor activity and body temperature rhythms were continuously recorded. One bunker was unshielded while the second bunker was shielded from the earth's natural E and B fields. Repeated experiments indicated that subjects living in the shielded bunker demonstrated significantly longer circadian periods than did subjects living in the unshielded bunker. Furthermore, intra-individual differences in period variability were increased in the shielded area and desynchronization between activity and body temperature rhythms was observed. Exposure to a 600-V/m DC E field in the shielded bunker failed to affect the period length but imposition of a much weaker AC field (2.5 V/m at 10 Hz) had the same effect on circadian activity as exposure to the earth's natural E and B fields. When the weak field was applied for 12-h on and 12-h off (Wever

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